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MEASUREMENT OF REGIONAL CIRCULATION BY THE LOCAL CLEARANCE OF RADIOACTIVE SODIUM

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THE dynamics of the blood-tissue exchange of a diffusible, inert substance has recently assumed significance as a basis for measurement of blood flow. The nitrous oxide method for the determination of cerebral blood flow[1] makes use of the time-concentration curves of this gas in arterial and cerebral venous blood. Where the tissue uptake of a substance is rendered measurable by the use of radioactive isotopes, it may be possible to estimate blood flow without resort to blood sampling. On this basis, measurement of peripheral blood flow has been proposed by Smith and Morales,[2] using radioactive krypton, and by Smith and Quimby,[3] using radioactive sodium. In both cases a mathematical analysis of the saturation curves in the forearm or foot for the purpose of calculating blood flow in these regions is rendered extremely difficult by the variety of tissues involved in the measurements. Smith and Morales were able to approximate quantitative results by assuming in their analysis a constant arterial concentration of radioactive krypton. When, however, the arterial curve is variable, as is the case with the intravenous administration of radioactive sodium,[3] mathematical analysis becomes almost hopelessly complex and requires, at best, a complicated integration involving the arterial curve obtained from serial blood samples. Smith and Quimby have not attempted an analysis of their sodium uptake curves but have employed them as a qualitative test of peripheral circulation. Both of these methods share the further disadvantages of exposing the entire body to radiation intensity equal to that necessary in the small segment under study, of requiring at least thirty minutes for a single measurement, and of being incapable of demonstrating rapid serial changes in blood flow.

If the diffusible tracer substance, instead of being administered in the general circulation, be introduced into the tissue in question, it is apparent that its clearance from the tissue will depend upon, and possibly be a measure of, the local tissue circulation. In fact, this very principle was utilized three years ago as a

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qualitative demonstration of the adequacy of local circulation.[4] The quantitative implications were not apparent to me until Dr. J. M. Crismon, of Stanford University, pointed out that in such a situation the arterial concentration might be neglected. On this basis I was able to make a simple mathematical analysis of the clearance of an injected substance.

Consider a small unit mass of the tissue into which the diffusible tracer (Na^{24} ion) has been injected. Let S represent its sodium space (extracellular volume); F_A, F_V, and F_L, the respective arterial inflow, venous, and lymphatic* outflow per minute; C_S, C_A, C_V, and C_L, the respective Na^{24} concentrations in S, arterial and venous blood, and lymph; and Q, the total content of Na^{24} in the unit mass of tissue.

In a short period of time (dt) there is a flow of venous blood ($F_V dt$) and of lymph ($F_L dt$) out of the tissue and a flow of arterial blood ($F_A dt$) into the tissues. The change in Q during this period would be equal to the quantity brought to the tissue by the arterial blood less the amount carried away in the venous blood and lymph or,

$$dQ = F_A C_A dt - F_V C_V dt - F_L C_L dt$$

The arterial concentration of Na^{24} will be negligible, representing a small quantity diluted by the entire cardiac output and, indeed, by the extracellular space of the body whence,

$$\frac{dQ}{dt} = -F_V C_V - F_L C_L$$

but $C_V = mC_S$ and $C_L = nC_S$

where m and n are constants with values between 0 and 1 and express the extent to which capillary blood and lymph come to equilibrium with the tissue concentration of Na^{24}. They depend on the diffusion rate of the ion, diffusion distances, capillary-tissue interface, on the proportion of arteriovenous shunts or other nonfunctional blood flow, and on the filtration and absorption of extracellular fluid at the capillary. Therefore,

$$\frac{dQ}{dt} = -F_V m C_S - F_L n C_S = -C_S (mF_V + nF_L)$$

but, $C_S = \frac{Q}{S}$, whence

$$\frac{dQ}{dt} = -Q \left(\frac{mF_V}{S} + \frac{nF_L}{S} \right)$$

which may be solved for Q:

$$Q = Q_O e^{-kt}$$

where Q_O represents an initial amount of Na^{24} and $k = \frac{mF_V}{S} + \frac{nF_L}{S}$

*In a previous description of this method[5] the author chose to neglect lymphatic drainage on the basis that it constituted a very small fraction of the total drainage. Its inclusion at this time makes the analysis somewhat more rigorous but does not change the fundamental concepts.

or the sum of the effective blood and lymph flow per volume of extracellular water of the tissue in question. Since F_V and F_L are both constant fractions, (r) and $(1\text{-}r)$, of F_A under any one set of physiologic circumstances, we have:

$$k = \frac{mrF_A + n(1\text{-}r)F_A}{S} = F_A\Theta$$

where $\Theta = \frac{mr + n(1\text{-}r)}{S}$ and represents the net effectiveness of the circulation as a renewal mechanism.

Thus, if the basic reasoning is valid, the tissue deposit of Na^{24} should decrease along a single exponential curve, which, if plotted semilogarithmically, should yield a straight line whose slope (clearance constant or k, above) is a quantitative measure of the total ability of the local circulation to remove and, by the same token, to supply freely diffusible substances.

METHOD

For testing the applicability of the theory developed above, the human gastrocnemius muscle was chosen as a suitable site. A small quantity of $Na^{24}Cl$ (5 μc. in 0.5 to 1.0 c.c. of isotonic saline) is injected at a depth of about 2.0 cm. into this muscle by means of a fine needle. A Geiger-Müller counter, shielded with 5 cm. of lead except for one face, is placed next to the calf with the opening directed toward the site of injection, and counts are recorded at one-minute intervals until the counts per minute become too low for significant measurement. Neither the dose injected nor the geometry of the system is critical so long as the relations between injection site and counter tube are preserved during any one measurement. The counts per minute less background (final plateau reached after clearance) and corrected for decay of Na^{24} are plotted semilogarithmically against time and a straight line drawn through the points. The slope of this line yields the value for k or,

$$k = \frac{\log C_1 - \log C_2}{.4343\ (t_2\text{-}t_1)}$$

where C_1 and C_2 equal counts per minute at t_1 and t_2, respectively. The time interval $(t_2\text{-}t_1)$ should be long enough to permit a valid average slope to be drawn (about ten minutes). If the circulation should change significantly during the clearance and the change persist for a period of several minutes, this will be reflected in a corresponding change in the clearance constant during that time.

RESULTS

In all cases where nothing was done to alter the circulation, the clearance followed a simple exponential curve (Fig. 1), indicating the validity of the theoretical derivation and the assumption on which it was based. In a small series of eight such clearances on the resting muscle in different individuals the mean clearance was 5 per cent per minute (Table I). This value for the normal

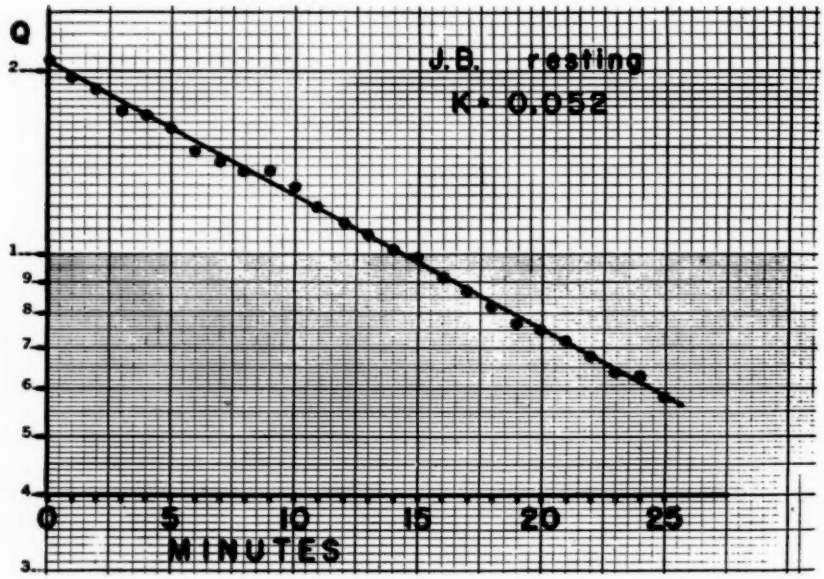

Fig. 1.—Counts per minute of Na^{24} plotted semilogarithmically against time for a normal resting human gastrocnemius. The actual counts have been divided by an arbitrary factor (in this case 3,200) for convenient plotting.

Na clearance of the human gastrocnemius has recently been confirmed by others.[6] To test the responses of the clearance constant to alterations in the circulation, some studies were done in which a control period was followed by some procedure designed to speed or slow the local circulation. The application of a tight tourniquet above the knee (Fig. 2, Table I) was invariably and immediately followed by a sharp reduction in the clearance constant to practically zero. Release of this tourniquet after ten minutes was associated with a clearance more than twice normal, undoubtedly a reflection of reactive hyperemia. Exercise of the gastrocnemius for one minute was accompanied and followed by a

TABLE I. GASTROCNEMIUS RADIOSODIUM CLEARANCE CONSTANTS

PATIENT	RESTING	TOURNIQUET	REACTIVE HYPEREMIA	AFTER 1′ EXERCISE
J. B.	0.052	0.000	0.077	0.142
A. C.	0.044	0.005	0.111	0.104
T. M.	0.046	0.000	0.133	
E. J.	0.066	0.002	0.173	
C. S.	0.065	0.005	0.104	
M. F.	0.033			
A. R.	0.064			
H. B.	0.033			0.092
Mean	0.050	0.002	0.120	0.113

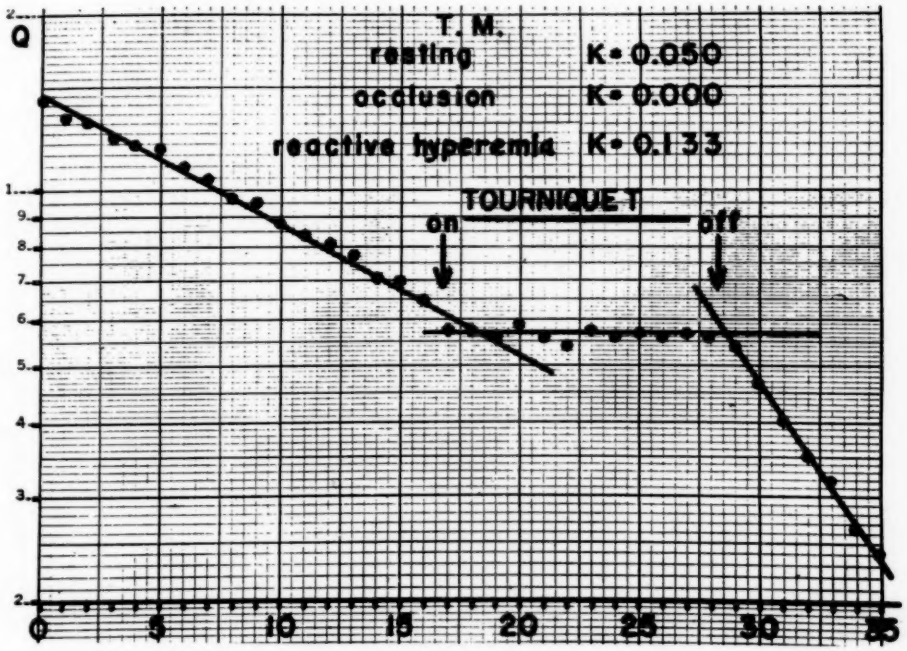

Fig. 2.—The effect of an arterial tourniquet about the thigh, and of reactive hyperemia on the clearance of Na^{24} from the human gastrocnemius.

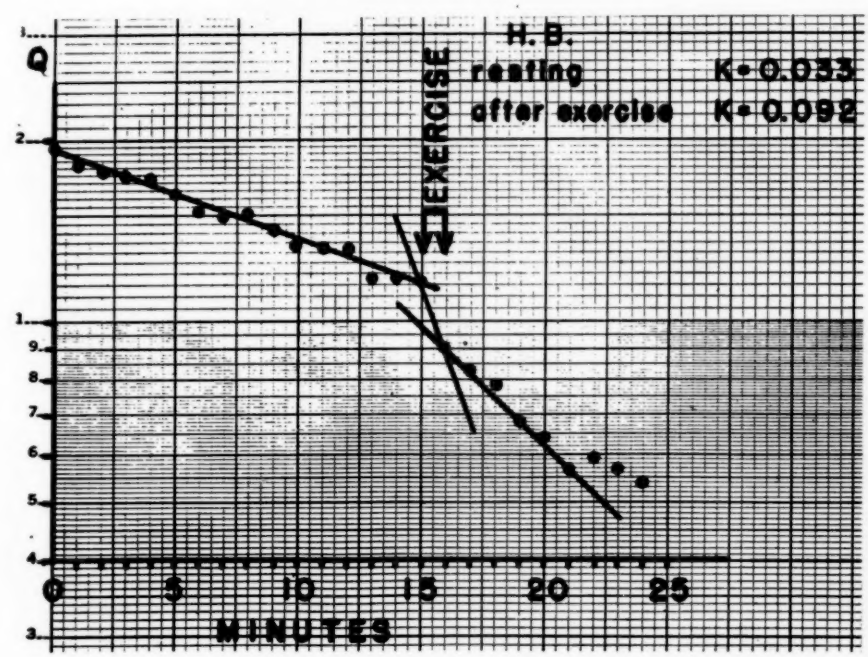

Fig. 3.—The effect on one minute's repetitive extension and flexion of the ankle on clearance of Na^{24} from the human gastrocnemius.

considerable increase in the clearance rate (Fig. 3, Table I). The local vasoconstrictor action of epinephrine was demonstrated by adding 0.1 mg. of the hydrochloride to the $Na^{24}Cl$ before injection. This resulted in a decrease in clearance to less than one-sixth the resting value (Fig. 4).

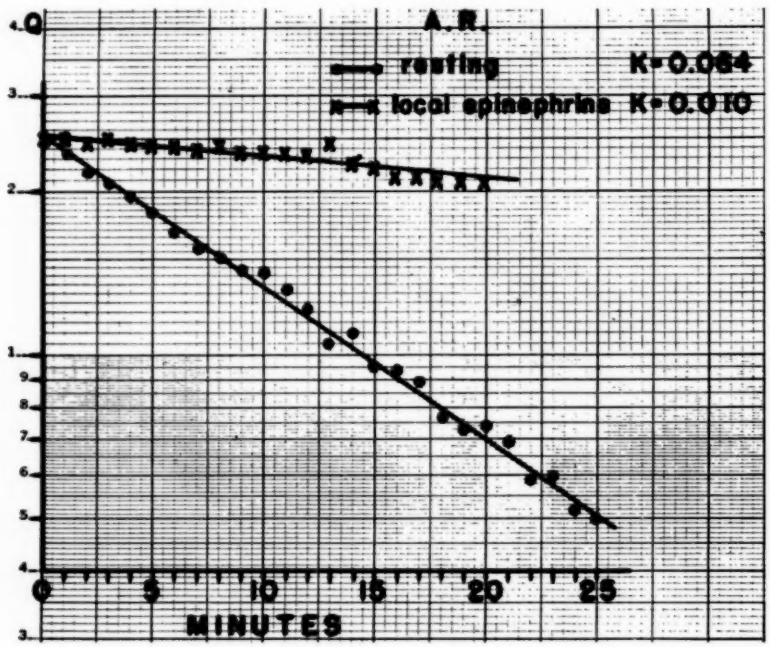

Fig. 4.—The effect on clearance of the addition of a small amount of epinephrine to the injected Na^{24} compared with the clearance of Na^{24} without added epinephrine in the same muscle.

DISCUSSION

The method appears to offer a convenient and clinically useful means for the measurement of effective circulation in a particular tissue. Since only about ten minutes are required for the accurate definition of a clearance rate and since a single injection permits twenty to thirty minutes of counting, it is possible to obtain at least two determinations from each injection. The infinitesimal dose of radioisotope required prolongs the useful life of the Na^{24} to the extent that an initial supply of 10 mc. may be used in these studies for nearly a week despite its very short half life of fifteen hours.

There is evidence to indicate that diffusion is of relatively little importance in the clearance of some tissues, in which case k would be an approximation to capillary blood flow. It seems preferable to the author, however, to retain the theoretical significance of k as a clearance constant rather than a rigorous measure of blood flow, a concession to exactness which does not compromise its value as a measurement of clinical importance. For intravascular blood flow is only one of

many factors involved in the homeostatic function of the circulation. In order to improve its nutrition a tissue may increase the flow of blood to itself but it is likely also to open closed capillaries, thus increasing diffusion interface and decreasing diffusion distances, or to increase filtration and resorption or accelerate the lymphatic circulation. It may well be argued that the effectiveness of the circulation in a tissue is better measured as its total ability to remove (and similarly to supply) freely diffusible substances. This total efficacy is accurately measured by the clearance constant, a concept which includes not only the volume flow of blood but also all the adaptations or disturbances which help or hinder the diffusion process. Although the sodium ion may be a less than vital contributor to cellular nutrition, its diffusion rate in aqueous systems is only slightly less than that of oxygen and carbon dioxide and more rapid than that of glucose,[7] making it a fair representative of these more important constituents.

Although this technique utilizes only one-twentieth the total dose of Na^{24} employed by Smith and Quimby[3] and therefore reduces proportionately the radiation throughout the body, it should be noted that the tissue immediately at the site of inoculation receives a considerably higher dosage. The most intense radiation is suffered by a sphere of tissue about 6 mm. in radius around the injection. With the help of a recent formula[8] the amount of this maximum radiation (including both beta and gamma) was calculated for this tissue at the average clearance of 0.05 and was found to equal 0.5 equivalent roentgens per μc injected, or a total of 2.5 equivalent roentgens when 5 μc are used. A less rapid clearance would increase this radiation dose in inverse proportion. Since an ordinary roentgenogram of the calf produces a radiation dose of from 3 to 5 roentgens, the maximum radiation dosage from the Na^{24} employed in a tissue quite insensitive to radiation does not appear to be excessive.

The technique described should be applicable to tissues other than the gastrocnemius; indeed, to any tissue accessible to a hypodermic needle. Its use in the skin (by iontophoresis), the heart, liver, and uterus is now under study.

SUMMARY

A method is described for determining the clearance of radioactive sodium from its site of injection in a tissue. It is theoretically predicted and empirically found that the sodium remaining at the site of injection decreases along an exponential curve, the slope of which, plotted semilogarithmically, is a constant called the clearance constant. It is suggested that the clearance constant represents a valid and convenient measure of the local circulation in its broadest sense, and therefore a clinically useful determination.

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ARTERECTOMY IN THE TREATMENT OF INTRACTABLE PAIN FOLLOWING RECOVERY FROM ACUTE ARTERIAL OCCLUSION

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IN DECEMBER, 1946, there was referred to us for study a physician who, two months previously, had had a myocardial infarction followed in two weeks by an acute occlusion of the left popliteal artery. This arterial embolus came on suddenly, with coldness, blanching, numbness, and paresthesia of the left foot and lower two-thirds of the left leg. Over the next two weeks the color and temperature changes gradually improved, but the paresthesias and numbness persisted, and gradually there was added to these a new type of pain which was continuous, diffuse, and subject to spontaneous, severe exacerbations, and which it was very difficult for the patient to describe accurately. Most often he would characterize it as cramping in character; at other times he said it felt like a burning sensation. He thought that it was unrelated to activity, temperature, or emotional states. It did seem to come on more often at night. When the acute, spontaneous attacks came on, he seemed to be able to get some relief by grasping the foot and rocking back and forth on his bed, or by getting up and walking to and fro across the room until stopped by pain in the left calf.

Physical examination showed a limb with severe impairment of arterial circulation, dependent rubor, distal hypoesthesia (see Fig. 1), with a delayed pain response to strong stimulation (protopathic pain response), and no evidence of increased vasoconstriction. A left lumbar block with procaine was done and, although the temperature of the left toes fell (see Fig. 2), the left foot felt easier and no pain occurred during or after the block, except to a minor degree. An arteriogram (Fig. 3) showed a filling defect, with obstruction of the left popliteal artery at the level of the superior geniculate branch.

Here we are dealing with a patient with acute occlusion of a major artery and ischemic neuritis with severe, spontaneous pain which had many of the characteristics of causalgia. This pain was somewhat improved by a sympathetic block with procaine, but skin temperature measurements showed a decrease in blood flow at the time of injection.

Last year we reported our experience with three patients who had sustained an acute occlusion of a major artery as a result of thrombosis.[1] All those patients actually fitted into the picture which we are now describing. They gave no clinical evidence of increased vasomotor tone, but in each one there was temporary

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relief of severe rest pain following lumbar block. We feel now that the terrific pain and hypersensitivity which they developed in the months following the acute occlusion might well have been due to ischemic neuritis or to some type of

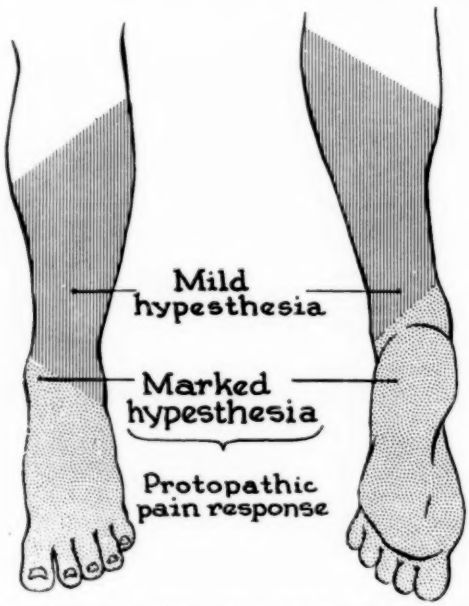

Fig. 1.—Sensory changes two months after acute arterial occlusion. Left popliteal embolus. December, 1946.

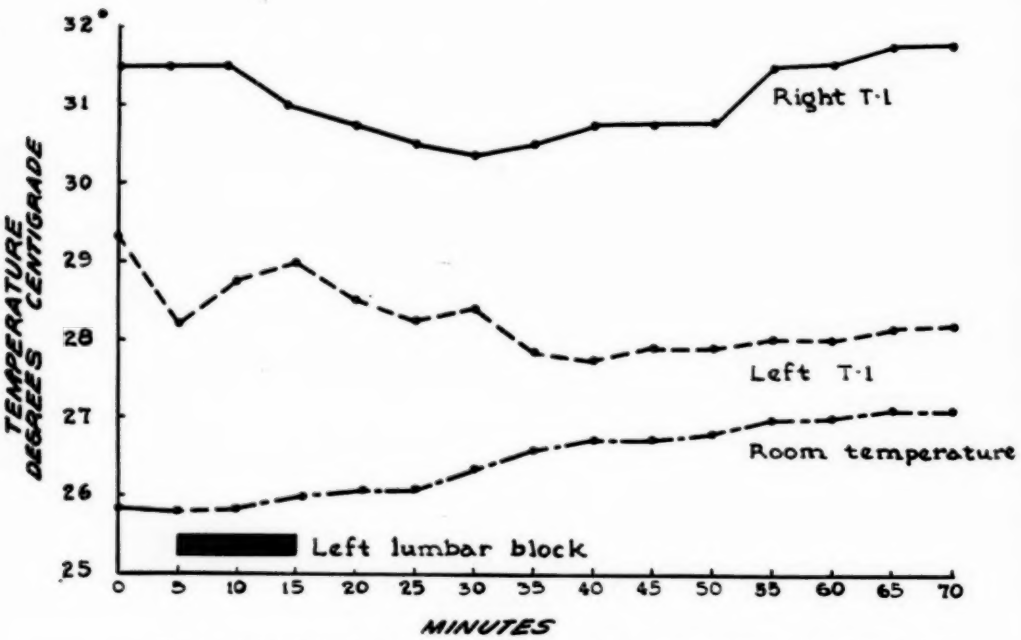

Fig. 2.—Lumbar block on skin temperature. Left popliteal embolus. December, 1946.

causalgia. In each case the relief of pain by lumbar block might have been attributed to the interruption of the sympathetic impulses, which is recognized to be effective in treatment of causalgia, rather than to any improvement in the supply of blood to the peripheral tissues. In each of these patients, lumbar sympathectomy was done, and brought relief of the rest pain of which they had complained. In each case, however, there was a rapid development of gangrene,

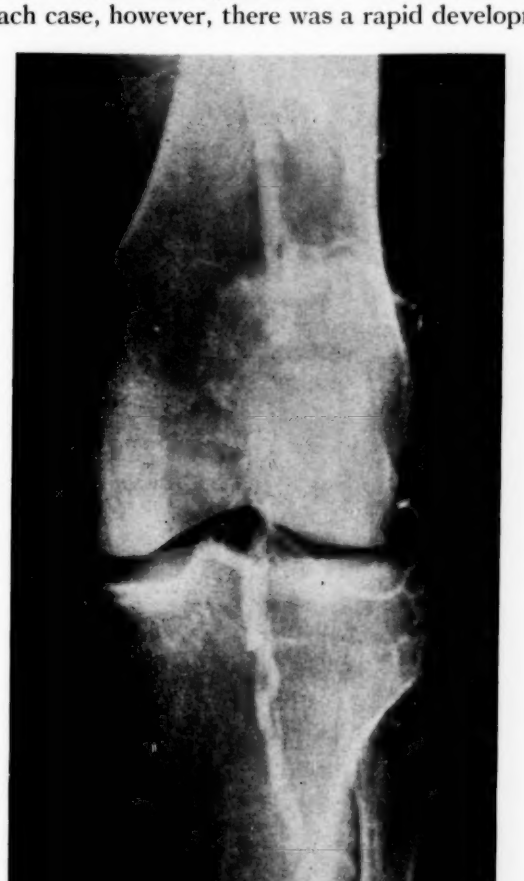

Fig. 3.—Filling defect with obliteration of left popliteal artery after embolic occlusion.

necessitating amputation of the involved leg. Similar cases have been described by Atlas.[2] We felt, therefore, that in the patient we are now discussing, lumbar sympathectomy, although it probably would have relieved the pain, was definitely contraindicated.

For the past twenty-five years Leriche[3] has recommended periarterial stripping and arterectomy. He advanced the hypothesis that the artery at the

TABLE I. THE SYMPTOMS, THE RESULTS OF STUDIES, AND THE RESULTS OF ARTERECTOMY IN ELEVEN PATIENTS.

PATIENT	ARTERY INVOLVED	ACUTE OCCLUSION	ISCHEMIC NEURITIS	PROTOPATHIC PAIN	DROP IN SKIN TEMP. WITH SYMPATHETIC PARALYSIS*	ARTERIOGRAPHY	ARTERECTOMY	RELIEF OF PAIN	OBJECTIVE IMPROVEMENT IN CIRCULATION	DEATH	AMPUTATIONS	FOLLOW-UP
1 C. G.	Left superficial femoral	+	+	+	0	+	None	0	0	0	0	24 mo.
2 P. S.	Left popliteal	+	+	+	+	+	Dec., 1946	+	0	4 mo.	0	4 mo.
3 W. L. B.	Right common femoral	+	+	+	0	+	Jan., 1947	+	0	0	0	17 mo.
4 A. McC.	Right popliteal	+	+	+	+	+	Feb., 1947	+	0	0	0	16 mo.
5 J. LeC.	Left superficial femoral	+	+	+	—	0	Sept., 1947	3 days	0	0	+	9 mo.
6 W. H.	Left superficial femoral	+	+	+	0	+	Sept., 1947	+	0	0	0	9 mo.
7 F. K.	Right common femoral	+	+	+	—	0	Oct., 1947	+	0	0	0	8 mo.
8 G. C.	Left superficial femoral	+	+	+	—	+	Nov., 1947	+	+	0	0	7 mo.
9 F. M.	Left superficial femoral	+	+	+	—	+	Jan., 1948	+	+	0	0	5 mo.
10 J. McE.	Right common femoral	+	+	+	—	+	Feb., 1948	+	0	9 days	0	9 days
11 M. C.	Right superficial femoral	+	+	+	0	+	May, 1948	+	0	0	0	1 mo.

*—means test not done.

site of occlusion may act as a trigger area for the production of pain and vasomotor disturbances. On the basis of this concept, a popliteal arterectomy was performed in our patient. The complete relief of the spontaneous pain was as surprising to us as it was gratifying to the patient. Postoperative studies failed to demonstrate objective improvement in the circulation. Numbness and paresthesia persisted. There was no improvement in intermittent claudication, but the patient was able to be up and around again. He returned to active practice until he died four months later of another myocardial infarction.

We have since then seen nine other patients with acute occlusion of a major artery, either by thrombosis or by embolism. The data on these patients are shown in Table I. There was recovery, as far as the viability of the extremity was concerned, in each case, but subsequently the patients developed intractable, diffuse pain and distal hypoesthesia, with a protopathic pain response. The pain was continuous, diffuse, and subject to severe spontaneous exacerbations. The patients described it variously as resembling a "toothache," or a "cramp," though they stressed that these terms did not quite describe the character of the pain. When asked to indicate how the pain differed from a toothache or a cramp, many of them mentioned the sensation of burning accompanying the pain. Some found relief in grasping the foot, and it was not unusual on ward rounds to find the patient gently rocking back and forth in the bed, tightly holding the affected foot. Dependency did not seem to help the pain. Walking appeared to ease it, though most of the patients stated that exercise was prevented by intermittent claudication. They all complained of numbness in the affected member. They all showed distal hypoesthesia and a delayed pain response, which Head has called the protopathic pain response. There was a peculiar emotional reaction to this delayed type of pain. The spontaneous pain seemed to be out of proportion to the degree of circulatory impairment. It might be relieved temporarily by lumbar sympathetic block.

With one exception, these patients have undergone an operative removal of the thrombosed segment. After operation there was relief of the severe spontaneous pain, though other types of pain due to ischemia might persist. Three of the patients spontaneously stated, a few minutes after the artery had been divided, that their pain was gone. One of the patients who had had such severe pain that he had requested an amputation, and who had slept only an hour at a time for almost a week, slept for sixteen hours immediately after the operative procedure. One patient had return of pain three days after the operative procedure, but stated that the pain was now different in character from that which he had experienced before surgery. This patient later developed severe venous thrombosis, with exacerbation of his arterial insufficiency, and a supracondylar amputation was necessary. Amputation of the leg was performed in only one other patient in this series. After arterectomy, although the spontaneous pain was relieved, this patient was incapacitated by hyperesthesia of the foot. There was marked atrophy of the soft parts, and a contracture of the knee developed. Two of the patients died from acute coronary occlusion, one of them nine days after surgery and the other four months after surgery. Neither of these, had had recurrence of his pain up to the time of his death. In one patient,

arterectomy was not done, but he has been treated with rest and vasodilators for two years. There has been no change in the character of his pain over this period of time.

The circulatory status of the affected limb was carefully evaluated in all these patients before and after surgery. In none of them has there been any objective improvement in the peripheral blood flow, although functional recovery in the postoperative period would suggest some improvement in circulation. In eight individuals there was no increase in the ability to walk, while in two there was some improvement over a period of months. The neurological findings have remained unchanged. There has been persistence of the subjective numbness and paresthia and persistence of the objective evidence of hypoesthia and the protopathic pain response.

Leriche[3] rightly classifies the arterectomy as a conservative measure. It is a relatively minor procedure and can be done even in the poor-risk patient. All of the operations have been done under local anesthesia. In most cases we were content to remove small portions (from 2.0 to 3.0 cm.) of the thrombosed vessel, although Leriche[3] has recommended removal of the entire thrombosed segment, up to 25 centimeters. The exact site of obstruction was accurately localized preoperatively by Thorotrast arteriograms. We preferred to use Thorotrast in these patients with impaired arterial circulation because of the danger of vasospasm produced by Diodrast. In two cases the artery was found to be occluded in the area which was exposed for arteriography.

DISCUSSION

Periarterial sympathectomy was first advocated for the treatment of posttraumatic vasospastic conditions by Leriche[4] in 1913. Subsequently he resorted to arterectomy in those cases in which the vessel was obliterated. He states: "It seems paradoxical to seek to improve the circulation in a limb which has been crippled by an arterial thrombosis by removing the obliterated segment." However, in spite of the circulatory arrest, after the thrombosed segment was removed, there was not only relief of pain but the quantity of blood reaching the periphery was augmented, the extremity became warmer, vasomotor disturbances disappeared, and, not infrequently, the pulse and oscillations reappeared. He feels that only one explanation is possible: the thrombosis modifies the state of the arterial wall, producing a state of centripetal excitation. He therefore defines an arterectomy as a sensory neurectomy which depresses the point of departure of vasomotor reflexes and permits the collateral circulation to achieve a state of vasodilatation. He feels that he has proved this experimentally through his work with Heitz.[5] Clinically, he points to his 45 to 50 per cent long-term good results in 144 arterectomies in elderly patients with arteriosclerosis.

Leriche[3] states that his worst results are in those patients with rubor and edema. His best results are in those who have intermittent claudication, rest pain, and rubor on dependency. He stresses the importance of preoperative arteriography, and feels that if in the arteriogram, the arterial segment distal to the thrombosis is not shown to be filled by the contrast medium, an arterectomy

would not be successful, but that if this distal segment is shown to be filled, the results will be excellent. He also stresses the importance of including all the thrombosed segment in the arterectomy, and he states that sometimes it is necessary to remove as much as 20 to 25 cm. of the superficial femoral artery. In our experience it has been necessary to remove only a short segment.

Recently Cooper[6] has reported a case of obliteration of the bifurcation of the aorta. Oscillometry and skin temperature studies showed improvement in the circulatory status of the lower extremities after the bifurcation of the aorta had been resected.

In the experimental animal, Strömbeck[7] was unable to demonstrate any significant increase in circulation after arterectomy. He produced thrombosis of arteries in dogs by means of trauma. Then, fifteen days to two and one-half months later, the segments were resected and arteriographic studies were done at intervals. Except in one case, no increased collateral circulation was demonstrated by arteriography.

In only two of our ten patients have we felt that there was objective evidence of increase in the circulation of the extremity after arterectomy. The improvement in circulation in these patients took place only some time after operation and was probably the result of a spontaneous increase in collateral blood flow. We do not believe that the relief of pain is the result of any improvement in circulation but rather that it is due to the interruption of some nervous reflex from the region of the thrombosed artery.

SUMMARY

After recovery from acute occlusion of a major artery to the extremity, even though the circulation is sufficient for tissue nutrition, the patient may develop severe rest pain with paresthesias and numbness of the extremity. This pain has been termed ischemic neuritis. Temporary relief may be obtained by blocking the sympathetic nerves to the leg, but sympathectomy is contraindicated. In a series of ten patients the site of obstruction was visualized by arteriography. Excision of a segment of the thrombosed artery was followed by immediate relief from the pain. There was no significant increase in circulation after this procedure. It is believed that arterectomy is of value in the treatment of this type of pain through the interruption of some nervous reflex which originates from the thrombosed artery.

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THE RELATIONSHIP OF ATHEROMATOSIS DEVELOPMENT IN THE CHICKEN TO THE AMOUNT OF CHOLESTEROL ADDED TO THE DIET

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ARTERIOSCLEROSIS of a type closely resembling that found in the human being appears spontaneously with advancing age in birds, as has been demonstrated by the classical work of Fox.[1,a,b] The susceptibility of birds to atherosclerosis has been demonstrated by the induction of atheromatosis in these animals by the feeding of diets high in cholesterol. Dauber and Katz[2,3] were the first to show that atherosclerosis could be consistently produced in the chicken by the feeding of a diet high in cholesterol. Since that time the chicken has been used by a number of investigators as a laboratory animal in the investigation of experimental atherosclerosis.[6,7] It possesses certain advantages for this type of research because atherosclerotic lesions can be induced in a relatively short time and the induced lesions resemble the spontaneously occurring ones in many respects. Furthermore, the chicken is an omnivore, and normally ingests cholesterol-containing foods, thus avoiding the important objection which has been leveled against the rabbit and the guinea pig, species in which cholesterol is essentially a foreign substance. Dauber[4] found that spontaneous arteriosclerosis developed in the chicken at the age of 5 to 6 months at the earliest: arteriosclerosis was found in 45 per cent of chickens over 1 year of age. It is obvious, therefore, that the chicken is a suitable animal for the experimental production of atherosclerosis if used before the age of 6 months, when spontaneous arteriosclerosis begins to occur. It is also a suitable animal for studies on the prevention of the spontaneously occurring disease.

Among the data which have accumulated to date, there are no studies undertaking to quantitate the effect of various concentrations of dietary cholesterol on the rapidity and degree of development of atherosclerosis in the chicken. Such information would obviously be of value in the establishment of controlled base lines for the carrying out of further special studies. Moreover, such studies might be of value in determining the degree to which the chick can dispose of dietary cholesterol. We have also utilized these studies to determine the relationship of dietary cholesterol concentration to the blood cholesterol levels and to ascertain the effect of various durations of such feedings.

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PROCEDURE

Four-week-old white Leghorn cockerels obtained from a commercial hatchery and known to be free of indigenous diseases were utilized. The animals were fed chick starter mash and tap water ad libitum for several days before the experiments were begun. Three series of experiments were run, lasting five, ten, and fifteen weeks, respectively. Each series consisted of five groups of twelve chicks each, making a total of fifteen groups and 180 chickens. In each series, the control group was maintained on chick starter mash and water. The four remaining groups received mash containing concentrations of 0.5, 1, 2, and 4 per cent cholesterol suspended in cotton seed oil, the oil making up 20 per cent of the diet by weight.

Animals were weighed weekly. Blood cholesterol determinations (total cholesterol) were made at weekly and biweekly intervals by the method of Schoenheimer and Sperry.[8] All animals were sacrificed, and the thoracic and abdominal organs were examined. The hearts and aortas were removed en bloc, slit open with a fine scissors, and any gross atheroma recorded on a diagram and fully described. In some cases the pulmonary arteries were opened and examined, and in a few birds the brain was removed en bloc to permit examination of the cerebral vessels. Sections were taken routinely from the lungs, liver, pancreas, adrenals, spleen, and kidneys. The thyroid glands were carefully dissected, cleaned, and weighed. Specimens were preserved in formalin, sectioned, and stained with hematoxylin and eosin in standard fashion. A longitudinal section consisting of heart muscle and thoracic aorta and a separate section of the abdominal aorta were made and examined in all birds in which there was no clear evidence of macroscopic atheromatosis. Sections were also made of the thyroid gland, liver, kidneys, and spleen in occasional cases.

GRADING

Atherosclerotic lesions were graded on the basis of their gross and of their microscopic appearance. The grading ranged from 0 to 4 and was based on the extent and severity of the lesions. The highest grades were given to extensive lesions, yellow in color, raised, and calcified on gross examination, or to those which showed marked calcification, cholesterol clefts, abscess formation, and many foam cells on microscopic examination.

The grading is, of course, subjective and empirical, but is consistent throughout when done by a single observer unaware of the particular experimental grouping of the animal being autopsied, as in this study. Experience proved that the gross inspection correlated closely with the microscopic appearance, and that gross grading was the more reliable method, as it precluded the possibility of the section being inadvertently cut from an uninvolved portion of the aorta.

Livers were classified as fatty when they were grossly yellow and greasy in appearance and on cut section. The microscopic examination consistently confirmed the gross diagnosis.

RESULTS

A. *Observations on the Vascular Lesions.*—

1. *The Effect of Five Weeks' Feeding of a Cholesterol-Rich Diet*: The data are summarized in Table I and illustrated in Figs. 1 and 2. Only three of the twelve chickens on 0.5 per cent cholesterol showed gross lesions of the aorta, and in each of these the liver was definitely fatty. There was evidence of fatty liver in only two other birds in this group. The gross appearance of almost all the aortas suggested slight thickening of the intima, but there was no yellow discoloration, nor were there any discrete plaques, and these aortas proved to be normal on microscopic examination. The average gross grading for this group was: thoracic aorta, 0.15; abdominal aorta, 0.

TABLE I. EFFECT OF FIVE WEEKS OF FEEDING OF CHOLESTEROL

CHOLESTEROL IN DIET (PER CENT)	THORACIC AORTA			ABDOMINAL AORTA		
	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO-SCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO-SCLEROSIS	AVERAGE GRADE*
Control	0	0	0	0	0	0
0.5	25	0–0.5	0.1	0	0	0
1	66	0.5–2	0.7	8	0–1	0.1
2	75	0.5–2	1.3	33	0–2	0.4
4	100	0.5–4	2.0	33	0.5–2	0.5

*4 = Severe.

Eight of the twelve birds on a 1 per cent cholesterol regime showed gross arterial lesions grading from 0.5 to 2. The liver was grossly fatty in all birds in this group. The vascular lesions ranged from irregular yellow streaking of the brachiocephalic vessels and aorta (classified as Grade 0.5) to discrete, raised, yellow plaques in the thoracic aorta (classified as Grade 2). Only one bird showed a lesion of the abdominal aorta, which consisted of several whitish pinpoint plaques. The average gross grading for this group was: thoracic aorta, 0.75; abdominal aorta, 0.10.

Nine of the twelve birds on 2 per cent cholesterol showed gross intimal lesions in the thoracic aorta, and four of these also had gross lesions in the abdominal aorta. All the animals had fatty livers. The lesions were more extensive and advanced than in the preceding groups. The average gross grading for this group was: thoracic aorta, 1.5; abdominal aorta, 0.5.

All the birds on 4 per cent cholesterol showed gross lesions of the thoracic aorta, ranging from Grade 1 to Grade 4 in classification. Four of these also had lesions of the abdominal aorta ranging from Grades 0.5 to 2. The liver was grossly fatty in all birds in this group, and many of the spleens showed whitish specks on cross section which proved on microscopic examination to be accumulations of foam cells. Some of the lesions were advanced. For example, in one

bird the brachiocephalic vessels showed numerous yellow, calcified plaques; the whole of the thoracic aorta was covered with a confluent pale yellow raised and ridged plaque; the semilunar valves showed marked involvement with thickening and plaque formation and there were also a few plaques on the mitral leaflets. The average gross grading for this group was: thoracic aorta, 2.0; abdominal aorta, 0.5.

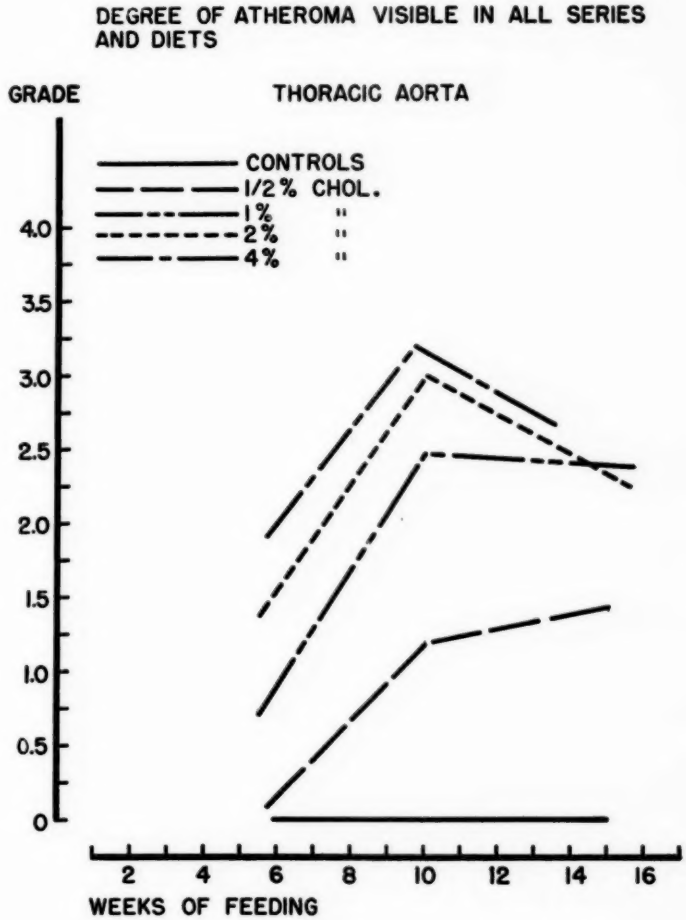

Fig. 1.

None of the birds in the control group showed gross lesions of the heart or aorta. The livers were normal in appearance, and no unusual findings in any of the other organs were observed.

To summarize, a progressive increase was found in the frequency of occurrence, severity, and extent of the lesions with increasing concentration of cholesterol in the diet. In the 0.5 per cent cholesterol group 25 per cent of the birds

had lesions in the thoracic aorta; in the 1 per cent group, 66 per cent; in the 2 per cent group, 75 per cent; and in the 4 per cent group, 100 per cent. There was a similar increase in the frequency of lesions in the abdominal aorta with increasing concentration of cholesterol in the diet. Thus, the percentage of animals showing gross lesions in the abdominal aorta ranged from 0 in the 0.5 per cent group to 33 per cent in the four per cent group. Gross atherosclerotic lesions

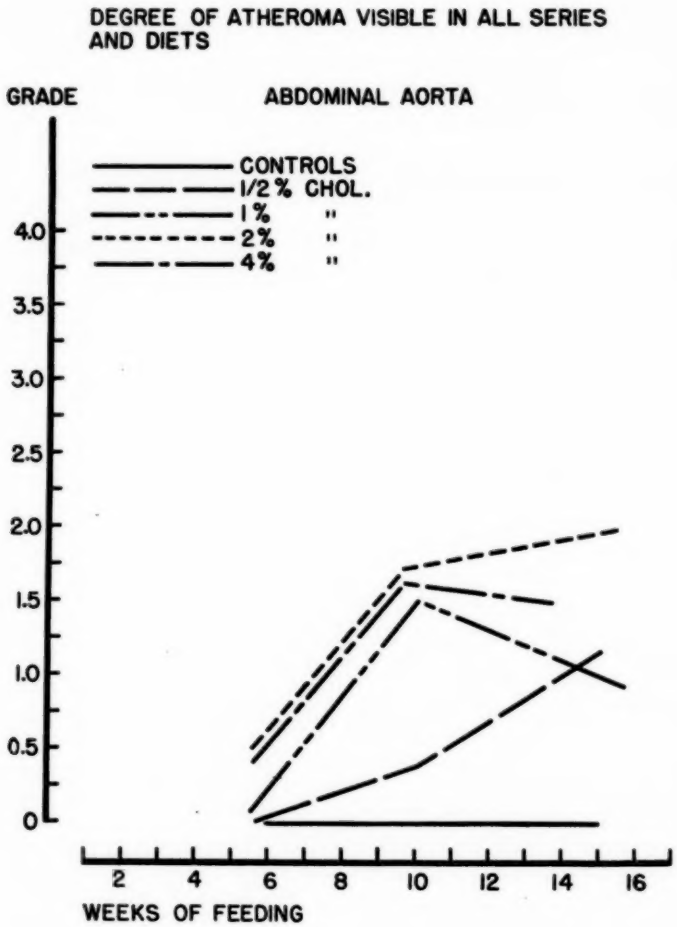

Fig. 2.

apparently can be produced in five to six weeks by the feeding of diets rich in cholesterol. The frequency of occurrence, severity, and extent of the lesions appears to be directly related to the concentration of cholesterol in the diet. Lesions of the abdominal aorta were less frequent and occurred only when the higher concentrations of cholesterol were fed.

2. *The Effect of Ten Weeks' Feeding of a Cholesterol-Rich Diet*: The data are summarized in Table II and illustrated in Figs. 1 and 2. As in the previous group fed for five weeks, there was an increased frequency of occurrence of lesions with increased concentrations of cholesterol in the diet. The 0.5 per cent cholesterol group showed 80 per cent of animals with lesions in the thoracic aorta, whereas all the other groups had lesions in the thoracic aorta in 100 per cent of animals. There was, further, a progressive increase in the severity of the lesions as shown by the empirical grading, which rose from 1.0 in the 0.5 per cent group to 3.5 in the 4 per cent group. The abdominal aorta showed a parallel increase in frequency and progression of lesions with increasing percentage of cholesterol, but as in the previous series, the time of occurrence and severity of abdominal lesions lagged somewhat behind the lesions of the thoracic aorta. None of the control animals showed atherosclerosis.

TABLE II. EFFECT OF TEN WEEKS OF FEEDING OF CHOLESTEROL

CHOLESTEROL IN DIET (PER CENT)	THORACIC AORTA			ABDOMINAL AORTA			PULMONARY ARTERY
	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHEROSCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHEROSCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)
Control	0	0	0	0	0	0	0
0.5	80	1–0.5	1.2	40	0.5–1	0.3	0
1	100	1–4	2.5	80	1–3	1.5	50
2	100	2–4	3.0	100	0.5–3	1.7	70
4	100	1–4	3.4	70	1–3	1.6	100

*4 = Severe.

All the cholesterol-fed chickens, with the exception of a few which died early in the course of this experiment, had grossly fatty livers. The pulmonary arteries were examined in several animals from each group of cholesterol-fed birds, and in some, small, white and yellow, hard, raised nodules were seen. The incidence of these lesions was greater in the groups receiving the higher cholesterol rations. The pulmonary arteries were examined in nine control birds and no lesions were found.

3. *The Effect of Fifteen Weeks' Feeding a Cholesterol-Rich Diet*: The data are summarized in Table III and illustrated in Figs. 1 and 2. The mortality in this group was relatively high, and the results summarized in Table III have been arranged to show the average values (a) for the entire group and (b) for those birds which survived eleven and one-half weeks or more of cholesterol feeding. Again it was observed that there was a tendency for increased frequency and severity of lesions with the higher concentrations of cholesterol. However, when these groups are compared with the preceding groups fed the same percentage of cholesterol for only ten weeks, it is apparent that the frequency of occurrence of lesions and their severity tend to be less after fifteen weeks than

after ten weeks of cholesterol feeding. This tendency was more marked in the thoracic aorta than in the abdominal aorta.

TABLE III. EFFECT OF FIFTEEN WEEKS OF FEEDING OF CHOLESTEROL

CHOLESTEROL IN DIET (PER CENT)	THORACIC AORTA			ABDOMINAL AORTA			PULMONARY ARTERY
	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHEROSCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHEROSCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)
Control	0	0	0	10	0.5	0.10	0
0.5	67	0.5–4	1.3	67	0.5–3	1.2	0
1	92	0.5–4	2.4	75	0.5–2	0.9	60
2	92	0.5–4	2.2	83	0.5–3	1.5	50
4	100	0.5–3	2.6	90	0.5–3	1.5	

*4 = Severe.

4. *The Effect of Duration of Cholesterol Feeding on Severity of Atheromatous Lesions*: We noted the occurrence of lesions after one and one-half to two weeks of feeding in one bird on a 1 per cent diet, in one on a 2 per cent diet, and in one on a 4 per cent cholesterol diet. These very early lesions were present in both the thoracic and abdominal aorta, and ranged in severity from slight to severe. In every case they were associated with the presence of a fatty liver.

TABLE IV. EFFECT OF DURATION OF FEEDING OF 0.5 PER CENT CHOLESTEROL ON THE DEVELOPMENT OF ATHEROMATOSIS

WEEKS FED	THORACIC AORTA			ABDOMINAL AORTA			PULMONARY ARTERY
	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHEROSCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHEROSCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)
5	25	0–0.5	0.1	0	0	0	
10	80	0.25–2	2.5	40	0.5–1	0.3	0
15	66	0.5 –4	1.3	66	0.5–3	1.2	0

*4 = Severe.

The relationship of degree of atherosclerosis with the time factor is shown in Tables IV to VII and in Figs. 1 and 2. These tables are organized to compare the effect of a given per cent of cholesterol in the diet when given over the three periods of time, namely, five, ten, and fifteen weeks. The four tables show a marked increase in the frequency and severity of atherosclerosis of the thoracic and abdominal aorta when the cholesterol feeding period was increased from five to ten weeks. This is true for each concentration of cholesterol used. Furthermore, in each instance, although the fifteen-week results were significantly

higher than those of the five-week group, they were not as high as those recorded for the ten-week period of feeding, as previously mentioned. This relationship holds even when the birds which died early in the fifteen-week series are excluded from the tables. This phenomenon will be discussed later when the effects on blood cholesterol levels and body weights are considered.

TABLE V. EFFECT OF DURATION OF FEEDING OF 1 PER CENT CHOLESTEROL ON THE DEVELOPMENT OF ATHEROSCLEROSIS

WEEKS FED	THORACIC AORTA			ABDOMINAL AORTA			PULMONARY ARTERY
	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO-SCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO-SCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)
5	66	0.5–2	0.7	8	0–1	0.09	
10	100	1–4	2.5	80	1–3	1.5	50
15	92	0.5–4	2.4	75	0.5–2	0.9	60

*4 = Severe.

TABLE VI. EFFECT OF DURATION OF FEEDING OF 2 PER CENT CHOLESTEROL ON THE DEVELOPMENT OF ATHEROSCLEROSIS

WEEKS FED	THORACIC AORTA			ABDOMINAL AORTA			PULMONARY ARTERY
	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO-SCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO-SCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)
5	75	0.5–2	1.3	33	0–2	0.4	
10	100	2–4	3.0	100	0.5–3	1.7	70†
15	92	0.5–4	2.2	83	0.5–3	1.5	60‡

*4 = Severe.
†Eight birds examined.
‡Five birds examined.

TABLE VII. EFFECT OF DURATION OF FEEDING OF 4 PER CENT CHOLESTEROL ON THE DEVELOPMENT OF ATHEROSCLEROSIS

WEEKS FED	THORACIC AORTA			ABDOMINAL AORTA			PULMONARY ARTERY
	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO-SCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO-SCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)
5	100	0.5–4	1.9	33	0.5–2	0.5	
10	100	1–4	3.4	70	1–3	1.6	100†
15	100	0.5–3	2.6	90	0.5–3	1.5	

*4 = Severe.
†Three birds examined.

An examination of these tables shows that, in general, atherosclerotic lesions in the abdominal aorta tended to occur somewhat later than those in the thoracic aorta and were less advanced. There was also a fair degree of correlation, by and large, between the severity of the lesions in the two portions of the aorta, although there were individual cases in which relatively severe lesions occurred in one portion of the aorta in the absence of any lesions in the other portion.

B. Observations on the Blood Cholesterol Levels.—

The data are summarized in Fig. 3. Blood cholesterol levels on the control birds varied within moderate limits throughout the experimental period, the

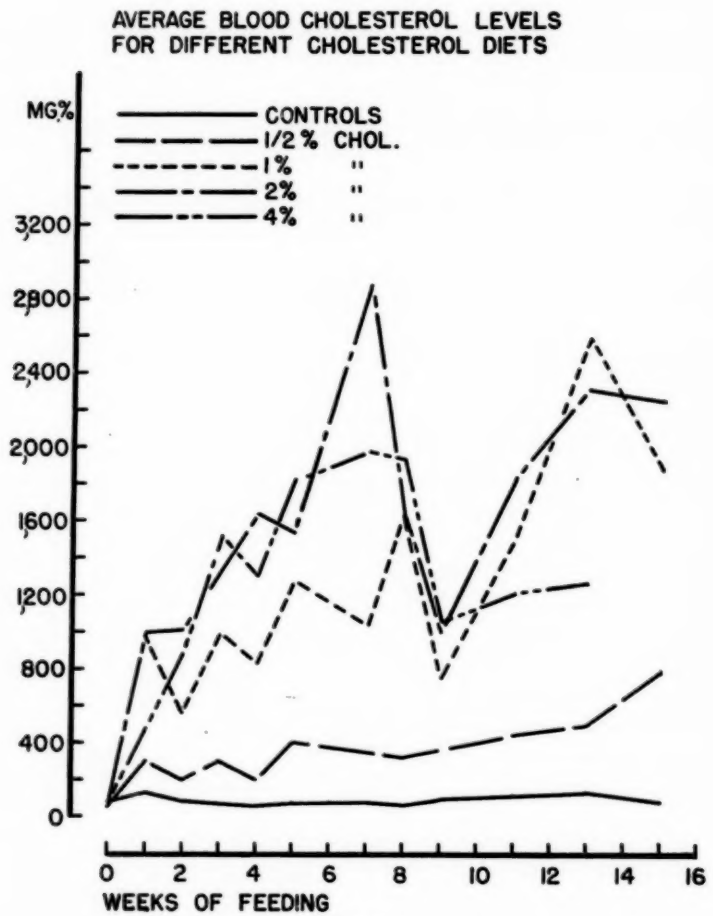

Fig. 3.

highest and lowest average readings for any week being 65 and 159 mg. per cent, respectively, and the average being 95 mg. per cent. The control values for *all* the birds in this study ranged from 34 to 108 and averaged 74 mg. per cent. The highest individual blood cholesterol recorded for any control bird was 274 mg.

per cent. This was definitely the exception, as the usual individual level was in the neighborhood of 80 mg. per cent. The blood cholesterol levels of the control birds varied from week to week but did not show any consistent trend with increasing age of the birds.

The chickens which received cholesterol all showed an immediate and marked increase in blood cholesterol after one week of feeding. This rise amounted to from six to twelve times the original levels. The smallest immediate increase was in the group receiving 0.5 per cent cholesterol, and amounted to a sixfold increase, from 51 to 312 mg. per cent. The greatest increase was in the 2 per cent group, which rose from an initial average of 81 to 1,003 mg. per cent in the course of one week. The 1 per cent group rose from 60 to 968 mg. per cent and the 4 per cent group from 96 to 471 mg. per cent.

During subsequent weeks, the 0.5 per cent cholesterol groups showed only a slight tendency to a further rise in blood cholesterol with continued feeding of cholesterol. There was a gradual rise to a maximum average value of 772 mg. per cent at the fifteenth week. The 1 per cent group showed an upward trend for the fifteen-week period. The maximum average value recorded in this group was 2,580 mg. per cent. There was a sharp dip to 769 mg. per cent at the ninth week, for which we have no explanation.

The 2 per cent group showed a steep rise in blood cholesterol levels to a high average value of 2,882 mg. per cent at the seventh week. Thereafter there was a marked decline to 1,003 mg. per cent on the ninth week and a secondary rise to 2,258 mg. per cent by the fifteenth week. By drawing a curve between the points (Fig. 3) it can be seen that the curve so obtained has a steep initial slope and then flattens out. This phenomenon was also observed in the group being fed 4 per cent cholesterol.

The 4 per cent group rose rapidly to a value of 1,540 mg. per cent by the third week, and then began a steady decline to 1,053 mg. per cent at the ninth week. The curve for this group shows a steep initial slope, a plateau, and then a fall. The correlation of this phenomenon with the data on weight and food intake is of interest in probing the reasons for this phenomenon and is discussed below.

The observations on blood cholesterol may be summarized as follows:

1. Feeding of cholesterol in dosages varying from 0.5 per cent to 4 per cent produced a marked rise in the blood cholesterol of from six- to twelvefold within the space of one week.

2. Feeding 1 per cent, 2 per cent, and 4 per cent cholesterol in the diet produced a sustained lipemia considerably greater than that produced by feeding 0.5 per cent cholesterol.

3. Diets containing 2 per cent and 4 per cent cholesterol resulted in a hypercholesterolemia which tended to decline toward the end of the fifteen-week period, whereas that produced by 1 per cent cholesterol showed a steady upward trend.

4. Diets containing cholesterol in excess of 0.5 per cent result in a lipemia which is marked, but not parallel to the further increases in the concentration of cholesterol in the diet. Thus, 2 per cent and 4 per cent of cholesterol produced about the same degree of lipemia as 1 per cent.

C. Observations on Body Weight.—

The data are summarized in Fig. 4. The animals were always amply provided with freshly prepared feed and water, and the differences in weight can therefore be taken to indicate differences in effective food intake. As we have not measured quantitatively the exact amount of feed ingested and the cholesterol content of the feces, we cannot discount the possibility of impaired absorption of ingested cholesterol from the gastrointestinal tract in birds fed a high-cholesterol diet.

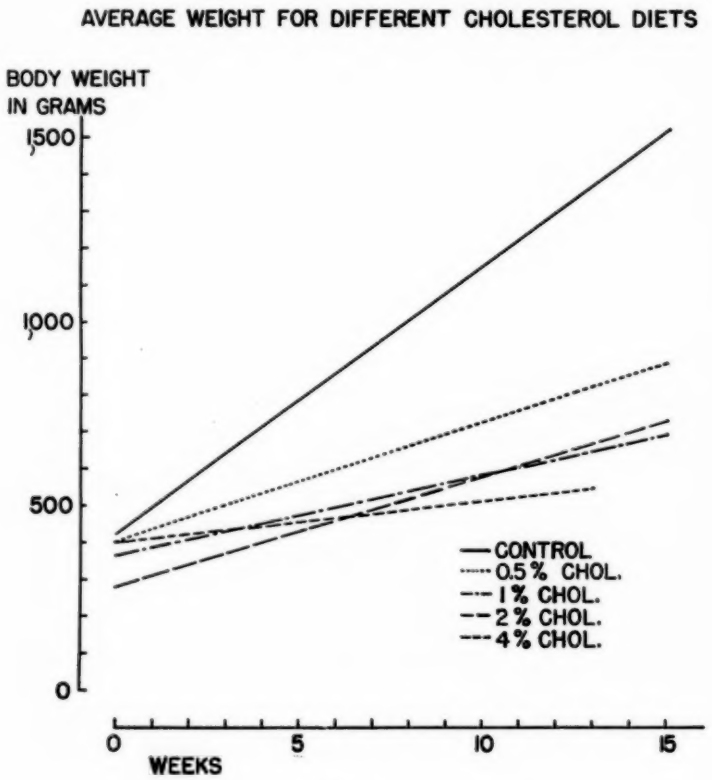

Fig. 4.

The control birds showed a steady rise in weight from an initial average weight of 423 grams to 1,509 grams at the conclusion of the fifteen-week period. The other groups were all significantly lower in weight, although there was a slight tendency for them to gain weight. The weight gain was most marked in the 0.5 per cent group and least in the 4 per cent group. The final average weight for the 4 per cent group was 484 grams, or only 70 grams more than the starting weight. It is apparent, therefore, that animals receiving cholesterol in amounts in excess of 0.5 per cent of their diet do not gain significantly in weight. This observation corroborates the findings of Dauber and Katz,[2,3] previously reported. They measured feed intake, and found a progressive decline in intake related to the

cholesterol content of the diet. The failure to gain in weight may therefore be due in part to a decline in food intake, the reasons for which are not apparent. We cannot exclude impaired intestinal absorption or even some faulty endocrine or metabolic mechanism.

DISCUSSION

Our results show clearly that in the chicken, at least, there is a direct relationship between the concentration of cholesterol in the diet and the frequency of occurrence and severity of atherosclerotic lesions which develop as a result of the feeding of cholesterol. There is also a direct relationship between the duration of the feeding period and the frequency of occurrence and severity of atheroma, at least for the first ten weeks of feeding. Thereafter, both frequency and severity of atheromatosis tend to decline. The reason for the lesser severity of the atherosclerosis after ten weeks of feeding is not clear. The decline in the blood cholesterol levels and the failure to gain in weight are correlative phenomena, but need not be the cause of the decreased severity of the atheromatosis. It is conceivable that only those animals with a superior ability to "tolerate" cholesterol survive beyond 10 weeks of feeding and hence the degree of atherosclerosis which they manifest is less.

There appears to be a correlation between the blood cholesterol levels and the degree of atheromatosis. This is most apparent in the five-week group, where there is a high degree of correlation. When ten weeks elapsed the frequency of occurrence of lesions for the 1 per cent, 2 per cent, and 4 per cent cholesterol-fed groups was about equal. This appeared to depend on the fact that the blood cholesterol levels of these groups were roughly similar. While the frequency of occurrence of lesions in all groups receiving over 0.5 per cent concentration of dietary cholesterol was roughly the same, the severity of the lesions was greater in the groups receiving the higher concentrations of cholesterol. This would indicate that the circulating blood cholesterol level is only a rough index to the progress of the atherosclerotogenic process. The time factor, however, cannot be neglected, since the continued feeding of 0.5 per cent cholesterol resulted in a steady increase in the number of animals with atheroma. This was associated with a rise in blood cholesterol level.

The feeding of cholesterol in amounts exceeding 0.5 per cent of the diet does not cause a continuous progressive rise in the blood cholesterol levels. After a few weeks a plateau is reached. This probably indicates that there is an upper threshold to the amount of cholesterol which the chicken can ingest, assimilate, and distribute from the gastrointestinal tract and that amounts in excess are probably excreted unchanged in the feces.

There can be no doubt that cholesterol feeding profoundly affects the appetite and well-being of the experimental animals. They are small, fail to gain in weight, lose their feathers, and in many instances become sick and die. The remarkably fatty livers which are found in all birds on high-cholesterol diets no doubt contribute considerably to this phenomenon.

Microscopic studies reveal that there is no essential difference between the vascular lesions seen in the chicken as a result of cholesterol feeding and those seen in atherosclerosis in man. Further, vascular lesions occur in the chicken in many organs. We have observed atherosclerotic lesions of all grades of severity in the aorta, heart valves, coronary arteries, and pulmonary arteries of the chicken. Similar lesions have also been found in the blood vessels of the spleen, adrenal and thyroid glands, and in the main renal arteries.

Careful histologic examination of sections of brain and kidney failed to reveal any atheromatosis of the renal arterioles or brain vessels.

Details of the histologic appearance of the vascular lesions have been described previously by Dauber and Katz.[3] We also found atheroma of the pulmonary arteries and of large veins, lesions which were not reported by them.

We wish to call attention to the occurrence of gross atheroma in our chickens after two weeks of feeding. To our knowledge this constitutes the shortest period of time for which cholesterol must be fed in order to obtain lesions. It takes thirty to forty-five days to produce microscopic atheroma and fifty-five to seventy-eight days to produce gross lesions in the rabbit.[5] Dauber and Katz[2,3] reported that the earliest intimal changes they observed in the chicken occurred at forty-two days of feeding, and the earliest gross lesions at forty-nine days.

It would appear, therefore, that atherosclerosis can be produced in the chick with as great, or greater, ease and rapidity than in the rabbit.

SUMMARY

1. The chicken, a member of the class *Aves*, possesses distinct advantages as an experimental animal in the study of atherosclerosis.

2. Feeding of cholesterol in concentrations of 0.5 per cent, 1 per cent, 2 per cent, and 4 per cent of the diet for periods of five, ten, and fifteen weeks was investigated.

3. There was a direct relationship between the concentration of cholesterol in the diet and the frequency and severity of the atherosclerosis which resulted.

4. There was a relationship between the duration of the feeding period and the degree of atherosclerosis produced for each concentration of cholesterol in the diet.

5. With concentration of cholesterol in the diet above 0.5 per cent, increasing the feeding period beyond ten weeks did not appear to lead to any increase in the amount of atherosclerosis.

6. Atherosclerosis occurred as early as two weeks after the commencement of feeding in our birds. The early occurrence of atherosclerosis in the chicken is related to the enormous increase in blood cholesterol which occurs during the first week of cholesterol feeding.

7. Amounts of cholesterol in excess of 0.5 per cent produce much the same degree of hypercholesterolemia, suggesting that there is an upper threshold for the assimilation of cholesterol.

8. There is a semidirect relationship between the degree of lipemia and the degree of atherosclerosis which is found.

9. A method for the consistent production of atherosclerosis in the chicken has been standardized for (a) varying concentrations of cholesterol in the diet, and (b) time course of feeding.

We are grateful to the following technicians and assistants for their help in carrying out these studies: Mrs. L. Havel (D. V. Dauber Memorial Research Assistant), Miss Marilyn Dudley, Miss Lorraine Adams and Mr. Grady Crowley. We are indebted to Dr. S. Rodbard for his valuable suggestions.

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THE CAUSE AND EFFECTS OF FLOW THROUGH DEFECTS OF THE ATRIAL SEPTUM

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ALTHOUGH it has long been known that the direction of flow through large defects of the atrial septum is from left to right, the reason for the direction of the shunt has received but little consideration until recently. According to White,[1] it seems generally to have been assumed that the left-to-right flow is due to higher pressure in the left atrium—this in spite of the fact that in experimental animals mean pressures in the two atria are approximately equal,[2] and in the absence of evidence to suggest that the situation in this regard is different in man.

In 1942 Uhley[3] proposed an attractive and logical theory which attributed the direction of the shunt to an effect of gravity, related to the cephalad location of the left atrium with respect to its fellow of the right side. Brannon, Weens, and Warren,[4] however, later reported that in two cases of atrial septum defect the oxygen content of blood obtained from the right atrium remained higher than that of vena caval blood during recumbency and in the head-down position, a finding which indicates that flow continued from left to right after the gravity effect had been eliminated or reversed.

More recently Stead and Warren[5] stated that the persistent left-to-right flow demonstrates that in cases of atrial septum defect pressure in the left atrium is higher than that in the right, and commented upon the seemingly paradoxical corollary that the right ventricle fills to a greater degree than the left ventricle, although right atrial pressure is less than pressure in the left atrium. They concluded that the reason for the large output of the right ventricle in this anomaly has not been determined.

Almost certainly, however, the reason for the left-to-right shunt (and the associated increase in right ventricular output) is to be found in the factors which determine the direction and the magnitude of flow through other apertures connecting adjacent chambers or vessels of the cardiovascular system such as ventricular septal defect, patent ductus arteriosus, and arteriovenous fistula.

THE DETERMINANTS OF FLOW BETWEEN ADJACENT COMMUNICATING VESSELS OR CAVITIES

The direction of flow through an ostium connecting adjacent vessels (or adjacent chambers of the heart) is determined by the magnitude of the resistance which, at the site of the communication, opposes the movement of blood into the

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natural channels pertaining to each of the communicating cavities: if the resistance opposing "natural" flow is unequal in the two vessels or chambers, blood will flow from the one in which resistance is greater into the other in which resistance is less.

The resistance to natural flow in each vessel depends upon the rate of flow into the vessel, its size in the region of the communication, and the anatomic features of the structures into which it normally leads. Resistance varies directly with the square of the velocity of flow, and inversely with the size of the vessel; with regard to the features of the structures into which the vessel leads, resistance is in general directly proportional to the length of these structures and inversely proportional to their cross-section areas.

Since pressure is a quantitative manifestation of resistance, it follows that the direction of flow through the communication is from the cavity in which pressure is higher into the adjacent cavity in which pressure is lower. However, if the ostium is of great size, a relatively large quantity of blood may be diverted through it even though the difference between the pressures on either side of the ostium is very small.

ATRIAL PRESSURES AND THE NORMAL RESISTANCES TO ATRIOVENTRICULAR FLOW

Rates of Atrial Inflow and Outflow.—In the normal subject the quantities of blood which enter and leave the right and left atria are necessarily equal over any considerable period of time. Inflow occurs continuously, but outflow is suspended during the period of ventricular systole. Flow into the ventricles is most rapid early in ventricular diastole, immediately after the opening of the atrioventricular valves.

Size of the Atria.—In the cadaver the right atrium of normal hearts is somewhat larger than the left,[6] but it is likely that the difference in their volumes is related to agonal and post-mortem accumulation of blood in the right side of the heart. During life the capacities of the two atria are probably about equal. Both atria and the great veins leading into them are readily distensible. The walls of the left atrium are one and one-half times as thick as those of the right.[6]

The Natural Channels of Atrial Outflow.—Each atrium leads via its atrioventricular opening, over the open atrioventricular valve into the cavity of its pertaining ventricle.

The right A-V opening is considerably larger than the corresponding orifice on the left side, "being sufficient to admit the ends of four fingers," while the mitral orifice admits "only two fingers"[6] (Fig. 1). The average circumference of the normal tricuspid orifice is one-fourth to one-third greater than that of the mitral opening,[7] and its cross area about 50 to 75 per cent greater. Therefore, the mitral orifice must offer more resistance to the passage of blood than does the tricuspid orifice.

Similarly, the inflow tract of the left ventricle is longer and narrower than that of the right ventricle; on the whole, the left ventricle is longer, and in cross section smaller, than the corresponding chamber of the right side[6] (Fig. 2).

These factors tend to produce greater resistance to the movement of blood toward the apex on the left side of the heart. It is also possible that the thicker walls of the left ventricle are more resistant to stretching than are the thinner walls of the right ventricle, so that near the end of diastole the resistance to filling may be greater on the left side. In addition, the tricuspid valve is more delicately constructed than the mitral valve, whose cusps are thicker and larger.[6] Because of this it is possible that the tricuspid valve opens more readily at the end of the postsphygmic period. Further, it is likely that during the period of rapid filling the three cusps of the more efficient valve of the right side lie in closer proximity to the walls of the ventricle than do the two cusps of the less efficient mitral valve, and hence impinge less upon the cavity of the inflow tract (Fig. 1).

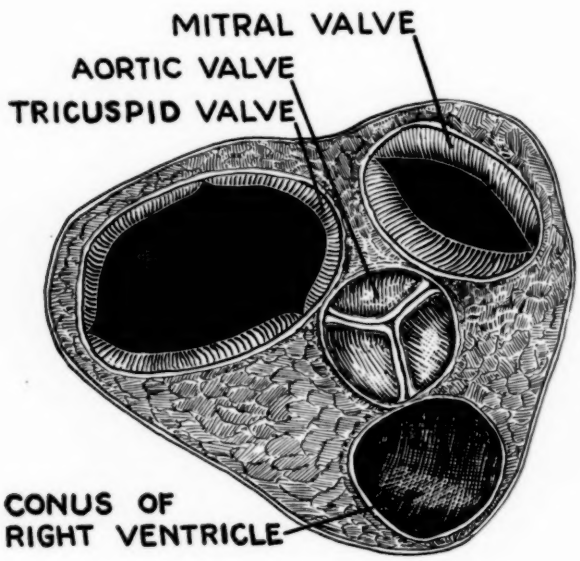

Fig. 1.—Schematic representation of the atrioventricular orifices and open atrioventricular valves, seen from above.

Atrial Pressures.—It appears, thus, that the resistance which normally opposes flow into the atria during ventricular systole is of about the same magnitude on the two sides, but that the resistance to atrioventricular flow is greater on the left side. It naturally follows that in normal subjects pressure in the two atria should be about equal during ventricular systole, but that during ventricular diastole pressure in the left atrium should exceed that in the right atrium.

This difference, however, is probably of small magnitude, for two reasons: First, both A-V orifices are of large size (the right roughly 10.5 square cm., the left 7.0), and both ventricles are almost empty of blood at the beginning of diastole.[8] The resistance opposing atrioventricular flow is then very slight on both sides, and the absolute difference as expressed by higher pressure in the left

atrium could hardly be very great. Second, the tendency toward the development of slightly higher pressure in the left atrium is probably counterbalanced by increase in the size of the readily distensible left atrium and pulmonary veins, so that pressure in the left atrium actually may exceed right atrial pressure only momentarily—at the beginning of the period of rapid ventricular filling and again during the brief period of atrial systole. The left atrium, slightly more distended than the right (and relatively hypertrophied) probably contracts with greater vigor, causing left atrial pressure momentarily to exceed pressure in the right atrium at this time.

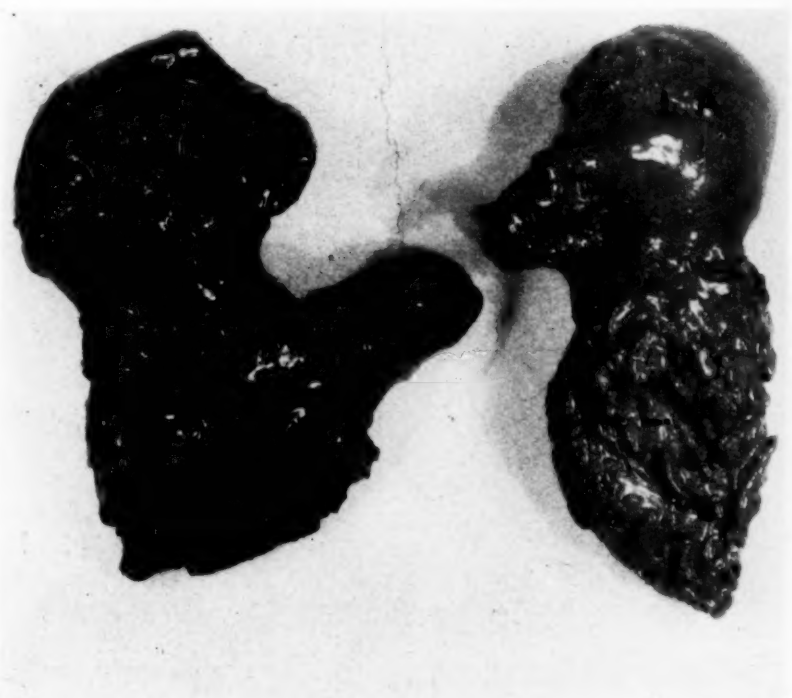

Fig. 2.—Casts of the cavities of a normal heart, viewed from their antiseptal surfaces. *R.A.*, right atrium; *R.V.*, right ventricle; *P.A.*, pulmonary artery; *L.A.*, left atrium; *L.V.*, left ventricle; L. aur., left auricle.

FLOW THROUGH DEFECTS OF THE ATRIAL SEPTUM

It seems certain that in most typical clinical cases the cardiovascular system was normal at birth except for the defect of the atrial septum, and that the other anatomic abnormalities result from the diversion of blood through the abnormal aperture. The hearts of normal infants (Fig. 3) possess anatomic features similar to those of adults, and it is likely that the tendency toward higher pressure in the left atrium appears shortly after the onset of respiration and functional closure of the ductus arteriosus; indeed, this tendency probably produces and

maintains functional closure of the foramen ovale. It is likely, therefore, that the factors concerned with flow through the septal defect begin to operate at an early age.

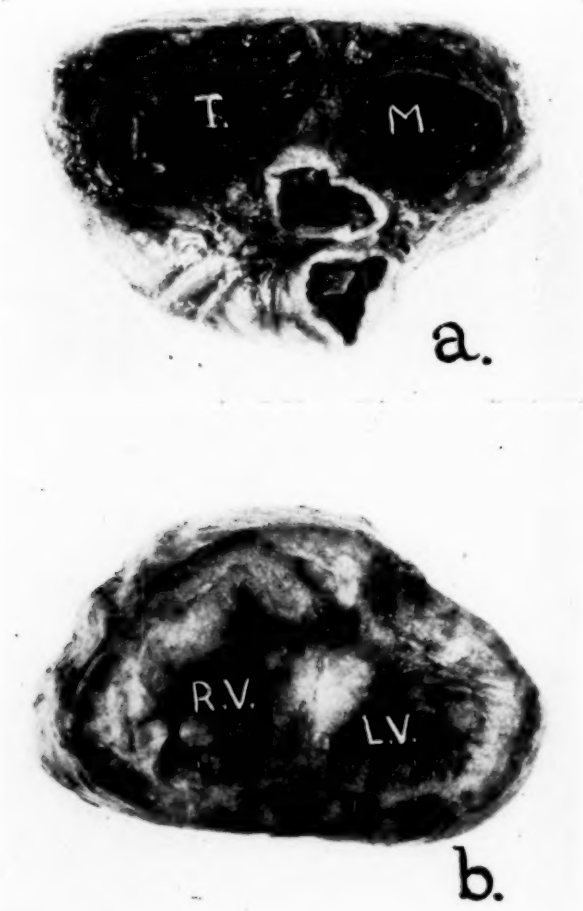

Fig. 3.—*a*, Cross section of the normal heart of a stillborn infant at term, in the same plane as that of Fig. 1. *T*, tricuspid orifice; *M*, mitral orifice. *b*, Section of same heart at a level 1.0 cm. below the atrioventricular orifices. *R.V.*, right ventricle; *L.V.*, left ventricle.

Direction of Flow.—In the beginning, when the tendency toward higher pressure in the left atrium initially appears, it would seem that little or no blood should flow through the defect during ventricular systole. During this period the atria are serving merely as readily distensible reservoirs, both of them capable of receiving considerable quantities of blood with only very slight increase of pressure, and each of them receiving the same amount of blood from the great veins which empty into it.

At the end of the postsphygmic period, as the A-V valves snap open and the period of rapid ventricular filling ensues, the anatomic factors concerned with resistance to atrial outflow come suddenly into play, and the resistance opposing flow into the natural outlet, the ventricle, becomes greater on the left side than on the right. Therefore, as blood begins rapidly to move out of the atria, a portion of the outflow from the left atrium is diverted through the septal defect into the right atrium; the normal tendency toward the attainment of higher pressure in the left atrium is counterbalanced by the shunting of blood into the right atrium, rather than by distention of the left atrium and its tributary veins. Blood continues to move through the interatrial communication until the resistances to atrioventricular flow have been equalized on the two sides, or until closure of the A-V valves with the onset of ventricular systole.

Early Dynamic Effects of the Shunt.— It is obvious that from the first a balance must be established whereby under any stable set of circumstances the output of each ventricle remains constant from beat to beat, and that so long as the heart remains competent the output of the left ventricle and, in turn, the rate of flow from the venae cavae into the right atrium will be maintained at normal rates. Since the blood shunted into the right atrium through the septal aperture is added to the normal caval inflow, it is clear that right atrial flow, right ventricular filling and output, and, in turn, pulmonary flow and the rate of flow into the left atrium are increased above the normal by the amount of blood which moves through the septal aperture.

In the beginning, as has been noted, there is no tendency for blood to flow through the defect during ventricular systole. However, once the shunting during ventricular diastole has begun, there is consequent increase of flow into the left atrium, which per se would cause this chamber to fill more rapidly during ventricular systole than its fellow. It is likely, therefore, that from the first, left-to-right flow through the defect occurs during both phases of the ventricular cycle, and, indeed, that the greater portion of the shunting occurs during ventricular systole, when the rate of caval flow into the right atrium is normal, but the rate of flow into the left atrium is increased.

Anatomic and Later Dynamic Effects.—The mean rates of flow through the two atria are equal, increased above the normal by the amount of blood which flows through the septal defect. However, outflow from the left atrium is divided into atrioventricular and interatrial portions, while the right atrium has only one channel of egress, the right ventricle. Moreover, blood flows out of the left atrium during both phases of the ventricular cycle, while outflow from the right atrium is suspended during ventricular systole. For these reasons, the average quantity of blood contained within the right atrium exceeds that contained within the left atrium, the difference in their contents being most marked near the end of ventricular systole; during each complete cardiac cycle the mean quantity of blood contained by the left atrium is only slightly above normal, while the amount contained by the right atrium is increased in proportion to the quantity of blood shunted through the septal opening. Therefore, the thin walls of the right atrium are subjected to abnormal stretching, while the left atrium is, on the average, no more than normally distended with blood; consequently, the right

atrium tends gradually to dilate more and more, while the cavity of the left atrium remains approximately normal in size.

As dilatation of the right atrium gradually progresses and comes to exceed physiologic limits, the increasing capacity of this chamber tends to reduce resistance to inflow, so that with the passage of time the quantity of blood shunted through the defect gradually increases, this increase in turn causing further dilatation of the right atrium. Thus, over the years gradual augmentation of right ventricular filling and output occurs, and the work of this chamber continues progressively to be increased.

Atrial Pressures.—Because of the ready distensibility of the atria and the subatmospheric pressure within the thorax, and because of the very slight resistance opposing the filling of competent ventricles, the atria are capable of receiving and transmitting quantities of blood greatly in excess of their usual quotas without increase of intra-atrial pressures. During strenuous exercise, for example, the stroke volume of the normal heart may be trebled and the minute output increased sixfold without increase of right atrial pressure.[9] It would not be expected, therefore, that atrial pressures should be altered significantly in cases of atrial septum defect, despite the fact that the quantity of blood entering each of the atria is considerably or markedly increased. Mean pressure in the right atrium and the form of the right atrial pressure curve have indeed been found to be normal (in the absence of congestive heart failure) in cases studied by us and by others.[4,10,12]

The existence of normal pressure in the right atrium in no way precludes increased filling of the right ventricle in cases of atrial septum defect. Atrial or "filling" pressure has nothing to do with the filling of a competent ventricle; the amount of ventricular filling and the size of the stroke volume are determined only by the quantity of blood contained in the appertaining atrium at the beginning of ventricular diastole, the quantity which flows into the atrium during the whole of this period, and to a minor degree by the power of atrial contraction. The lack of correlation between atrial pressure and ventricular filling does not necessarily indicate, as Stead and Warren[5] have suggested, that the ventricle dilates actively in order to receive more blood and thus to increase its output; but, rather, testifies to the very slight resistance opposing passive filling of competent ventricles, which allows maximal filling and output without elevation of atrial pressures above the levels recorded under basal conditions. Only when the ventricle has become incompetent, and the amount of its residual blood considerably increased, does the resistance opposing ventricular filling increase sufficiently to cause elevation of atrial pressure.

Indeed, it seems probable that right atrial pressure may not exceed normal limits in cases of atrial septal defect, even if the compensating right ventricle fails to cope adequately with the augmented venous return incident to muscular activity. During exercise the circulation rate increases without change of the balance between pulmonary and systemic flow so long as the right ventricle remains competent; right ventricular output, the quantity of blood diverted through the septal opening, and left ventricular output, increase in the same

proportion. However, as compensation of the right ventricle fails, the balance is temporarily disturbed: residual blood in the right ventricle increases, its output falls off, and right atrial pressure is increased because of the accumulation of blood in this chamber.

But consequent to the reduction of right ventricular output, filling of the left atrium is diminished, with a resultant tendency toward decline of left atrial pressure. The resistance opposing left-to-right flow through the shunt is therefore increased in relation to the resistance offered to flow into the right ventricle, and the magnitude of the interatrial shunt is thereby reduced. Total flow into the right atrium then decreases, right atrial pressure declines, and the burden of the right ventricle is lessened so that its output may now keep pace with the rate of its filling; compensation is restored because the decrease in the magnitude of the shunt exceeds the reduction in the output of the failing ventricle. Although the fraction of left atrial outflow which enters the left ventricle increases as the right ventricle fails, it appears that in many cases the absolute quantity of blood entering the left ventricle (and consequently the output of this chamber and the rate of systemic flow) is subnormal under conditions of usual daily activity, as attested by the frequent finding of a hypoplastic aorta.[11]

By this unique train of events, incipient cardiac decompensation promptly results in decrease of the heart's burden without abnormal elevation of venous pressure, and with relatively slight reduction in the blood supplied to the tissues of the body. The frequent absence of symptoms in the presence of pronounced physical signs, the active, useful lives which many of these persons have led, and the not uncommon attainment of ripe old age[11] may thus be explained.

Whether left atrial pressure actually remains normal or near normal in cases of defect of the atrial septum is, of course, not known, for pressure has never been measured in this chamber of the normal human heart; even in experimental animals accurate estimation of left atrial pressure is difficult because of artifacts produced by movements of the heart and other factors. The fact that dilatation of the left atrium fails to occur, even in cases of Lutembacher's syndrome, is, however, strong indirect evidence against great increase of left atrial pressure.

In several cases studied by venous catheterization the catheter entered the left atrium via the septal defect, so that it was possible to obtain recordings or readings of pressures in this cavity. In Brannon, Weens, and Warren's[4] case it appeared that pressure in the left atrium was somewhat higher than that in the right, but the pressure recording from the left atrium was distorted by large artifactual oscillations. In the case studied by Dexter and associates,[10] mean pressure in the left atrium seemed to exceed right atrial pressure by 4.0 mm. of mercury. In three cases recently reported by Cournand and associates,[12] mean pressure was higher in the left atrium by 4.0, 1.6, and 2.5 mm. Hg, respectively, and the fluctuations of the manometer were of much greater amplitude when the tip of the catheter was in this chamber.

Whether the pronounced fluctuations recorded in Cournand's cases (about 22 mm. Hg between maximal and minimal pressures during a single cardiac cycle in one case) accurately express actual changes of left atrial pressure is, however,

uncertain. They may have resulted in part from artifactual, local changes of pressure related to movements of the catheter tip as currents of blood impinged against it or as the heart moved or the atrium contracted, or related to the "velocity head"[9] of currents directed toward or away from its aperture. The very magnitude of the fluctuations—exceeding the amplitude of the pressure pulse in the pulmonary artery of normal individuals (12 to 20 mm. Hg), and almost equalling the pulmonary artery pulse pressure in one of Dexter's[10] cases of atrial septum defect (25 mm. Hg), in which the interatrial shunt was estimated as 65 per cent of left atrial inflow—suggests the possibility of artifactual influences. Further, it is difficult to understand why, in the presence of free interatrial communication, such sharp changes in left atrial pressure should fail to affect the form of the right atrial pressure curve, especially during systole of the atria, at a time when the volume of the contracting right atrium is decreasing, its walls are maximally resistant to distention, and the resistance to atrioventricular flow is greatest.

Cournand and his associates[12] suggest that in normal man the pressure relationships between the two atrial cavities may be similar to the curves recorded in their cases of atrial septum defect, and attribute the differences in mean and instantantous pressures to three factors: lesser distensibility of the thicker-walled left atrium, smaller capacity of the venous reservoir of the lesser circulation, and more pronounced effects of ventricular activity upon volume and tension in the left atrium than in the right. They suggest also that the same factors are responsible for the shunting of blood through defects of the atrial septum.

The opinion that normal differences between pressures in the right and left atria are due primarily to differences in the anatomic features of the two sides of the heart, and that the same factors are responsible for flow through defects of the atrial septum, is in accord with the general concept presented in this paper. It is doubtful, however, that the factors suggested by Cournand and associates are of prime importance in atrial pressure relationships. There is no reason to believe that within limits hypertrophied muscle fibers resist stretching more than nonhypertrophied fibers, and therefore it is unlikely that the left atrium offers appreciably greater resistance to inflow than does its fellow, except perhaps momentarily at the end of the phase of rapid atrial filling. The effective, intrathoracic reservoir of the caval system is hardly more capacious than the pulmonary venous system, although the four pulmonary veins, because of their relatively small individual calibers, may afford less protection than the larger venae cavae against factors (such as atrial contraction) which tend to cause abrupt increase of atrial pressure. The thicker, firmer cusps of the mitral valve[6] and the larger, stronger papillary muscles inserted into its chordae tendinae should serve to mitigate the effects of the powerful contraction of the left ventricle upon volume of, and pressure in, the left atrium.

Pulmonary Arterial Pressure.—The increase in the rate of blood flow through the lungs tends of itself to cause elevation of mean pressure in the pulmonary arteries; per se, an interatrial shunt amounting to half of the left atrial inflow, with consequent doubling of the right ventricular output, would result in a fourfold increase of mean pulmonary arterial pressure. The tendency toward the develop-

ment of such marked hypertension is opposed by the existence of the septal defect itself, which acts to reduce the total resistance of the lesser circulation, and is in part counterbalanced by progressive dilatation of the pulmonary arteries, which has a similar effect upon resistance—directly, because of the increased size of the vessels, and indirectly, because of the resultant diminution in the linear velocity of flow. These mitigating factors cannot be expected to prevent, over the years, gradual and progressive elevation of mean pulmonary arterial pressure to definitely hypertensive levels. As in other instances in which mean arterial pressure is elevated because of increase in ventricular stroke volume,[9] there occurs relatively great elevation of the systolic pressure and much less pronounced rise of the diastolic. Pulse pressure is consequently increased, and the pulse wave rises and falls more quickly than is normal; these features of the pulse wave account for the throbbing of the pulmonary arteries observed fluoroscopically in clinical cases—the characteristic "hilar dance."

It is to be noted that although in proportion to the increase of mean pressure the rise of diastolic pressure is of relatively small magnitude, diastolic pressure is necessarily increased above normal or usual levels unless there is only slight elevation of mean pressure. Thus, it is not necessary to assume the existence of increased "peripheral resistance" in the pulmonary circuit in order to explain the occurrence of slight or moderate elevation of the pulmonary diastolic pressure. All the features of the pulmonary hypertension observed in cases of atrial septal defect[4,10] are adequately explained as effects of an augmented output of the right ventricle, provided allowance is made for the relatively wide ranges of pulmonary arterial pressures recorded in normal subjects by techniques employing cardiac catheterization. If the shunt is of considerable magnitude, one should expect definite but not marked elevation of mean pressure in the pulmonary arteries, great increase of pulse pressure, striking elevation of systolic pressure, and slight or moderate elevation of diastolic pressure.

SUMMARY

The reason for the shunting of blood from left to right through large defects of the atrial septum has been sought in a consideration of the factors which determine the direction of flow through other abnormal apertures connecting adjacent vessels or adjacent cavities of the heart. This consideration leads to the conclusion that the direction of the interatrial shunt is due to differences in the normal anatomic features of the atrioventricular orifices and the ventricles of the right and left sides of the heart.

The mitral orifice is the smaller, the tricuspid the larger of the two atrioventricular openings. The cavity of the left ventricle is longer and narrower than that of the right ventricle, which is shorter and in cross section larger than its fellow. These differences (and perhaps also the thicker walls of the left ventricle and the less efficient operation of the mitral valve as compared with that of the tricuspid valve) are responsible for greater resistance to the flow of blood from atrium into ventricle on the left side of the heart, with a consequent tendency toward the attainment of higher pressure in the left atrium than in the right

atrium during the period of ventricular diastole. Although this tendency is in large part counterbalanced in normal subjects by distention of the left atrium and pulmonary veins, it is considered sufficient to initiate the movement of blood from the left atrium into the right through a large defect of the atrial septum.

Once the interatrial shunt is initiated, a train of effects naturally ensues whereby flow through the defect occurs during both phases of the ventricular cycle and gradually increases in amount, and filling and output of the right ventricle are progressively augmented, with corresponding increase in the rate of pulmonary flow and consequent elevation of pulmonary arterial pressure. Progressive dilatation of the right atrium, dilatation and hypertrophy of the right ventricle, and dilatation of the pulmonary arterial tree develop along with the gradual increase in the magnitude of the shunt, but the left atrium escapes enlargement because of the additional channel of outflow provided by the septal defect.

Atrial pressures remain normal because of the ready distensibility of the atria and great veins, the negative intrathoracic pressure, and the very slight resistance which opposes the filling of competent ventricles. Even if the right ventricle fails to cope adequately with the augmented return incident to unusual or ordinary activity, it seems likely that resultant decrease in the relative magnitude of the interatrial shunt quickly limits the burden imposed upon the right ventricle and prevents abnormal elevation of right atrial and venous pressures.

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PENICILLIN THERAPY OF CARDIOVASCULAR SYPHILIS

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THE use of penicillin in the treatment of cardiovascular syphilis followed the successful use of this antibiotic in other forms of syphilis. With its use the fear of damaging Jarisch-Herxheimer reactions arose promptly, and it was not long before a few warning notes appeared in the literature. Dolkart and Schwemlein[1] reported the necessity of discontinuing penicillin in two patients because of untoward reactions. A review of these two cases, however, reveals that one patient had rheumatic heart disease and experienced anginal episodes after receiving 20,000 units of penicillin. He had received one injection of 10,000 units on each of the preceding two days without untoward reaction. The second patient noted precordial pain on the fourth day of penicillin, after a total of 700,000 units had been administered. He had had previous bouts of precordial pain seven and six years earlier. The relationship of penicillin to these symptoms is not a clear one.

Moore[2] reported the death in heart failure of one patient four days after the onset of combined malaria and penicillin therapy. Autopsy revealed plaques of aortitis with large hemorrhages in each. Callaway and coauthors[3] reported the probable rupture of an aortic cusp in one of their patients several weeks after the completion of penicillin therapy. The latter accident might have been due to a therapeutic paradox secondary to the healing of the syphilitic inflammation, but we agree with Tucker and Farmer[4] that there is little evidence that the phenomena described were due to Herxheimer reactions.

Russek and coauthors,[5] Hill,[6] and Tucker and Farmer[4] have reported on penicillin therapy in a total of forty-six patients with cardiovascular syphilis in whom no adverse reactions were noted. Our own observations are in accord with the reports of these authors.

In the experience of one of us (E. W. T.), no harmful Herxheimer reactions during the treatment of cardiovascular syphilis have been noted in the past twelve years. For this reason, perhaps, Herxheimer reactions were feared less than on other services[2,7] where extreme caution has been urged in the treatment of patients with cardiovascular syphilis. Nevertheless, it was thought advisable, in patients who had not received previous antisyphilitic therapy, to start treatment with a preparation less rapidly spirocheticidal than penicillin. For

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TABLE I. PATIENTS WITH AORTIC INSUFFICIENCY

PATIENT	SEX	COLOR	AGE ON ADMISSION	AGE AT CARDIAC DIAGNOSIS	C.N.S.* DIAGNOSIS	KNOWN DURATION OF SYPHILIS	PREVIOUS ANTISYPHILITIC TREATMENT	CARDIAC SYMPTOMS	DIMINISHED CARDIAC RESERVE	PRECORDIAL PAIN	PAROXYSMAL DYSPNEA	CONG. HEART FAILURE	DIGITALIS	MERCUR. DIURETICS	PENICILLIN (IN MILLIONS OF UNITS)	DATE	PRELIMINARY BISMUTH	FOLLOW-UP
Al	M	B	58	54	—	Adm.	0	5 yr.	+	+	+	+	+	—	6.0	4/47	2	Imp.†—10 mo.
Ba	M	W	34	34	M.V.	12 yr.	Adeq.	—	—	—	—	—	—	—	4.3	4/46	0	Imp.—22 mo.
Br	F	B	52	52	—	Adm.	12 Bis.	?	—	?	—	—	—	—	5.0	8/47	0	Same—6 mo.
Bu	M	B	37	37	T.P.	2 yr.	Adeq.	—	—	—	—	—	—	—	4.0	4/45	0	——
Ce	M	W	65	65	T.P.	3 mo.	15 Bis.	—	—	—	—	—	—	—	6.0	4/46	0	Died—12 mo. (postoperative)
Ch	M	Y	54	50	T.D.	3 mo.	12 Inj.	3 mo.	+	—	+	—	—	—	6.0	5/46	0	Worse—20 mo.
Da	M	B	47	47	A. N. S.	30 yr.	Inadeq.	On adm.	+	—	—	+	—	—	6.0	3/46	0	——
Ed	M	W	49	48	T.P.	Adm.	0	1 yr.	+	+	—	+	+	+	3.0	7/44	0	Died—2 mo. (C.H.F.)‡
Fa	M	W	56	?	M.V.	20 yr.	Inadeq.	+	+	—	+	+	+	+	6.0	7/47	1	——
Hor	F	W	37	37	(Preg.)	2 yr.	Inadeq.	+	+	—	—	—	—	—	4.0	11/45	1	Died—14 mo. (cause unknown)
How	M	W	52	52	T.D.	Adm.	0	—	—	—	—	—	—	—	6.0	6/47	0	——
Jo	F	W	59	58	—	1 yr.	15 Bis.	1 yr.	+	+	—	—	—	—	4.0	2/47	0	Imp.—12 mo.
Ka	F	W	40	40	—	4 mo.	0	5 mo.	+	—	—	—	—	—	5.0	6/47	3	Imp.—8 mo.
Le	F	B	53	53	—	Adm.	0	1 mo.	+	—	—	+	+	+	3.2	6/46	3	Died—5 wk. (C. H. F)
Mc	M	B	58	56	—	43 yr.	Inadeq.	2 yr.	+	+	+	+	+	+	5.0	12/47	0	——
Mo	M	P. R.	52	50	T.D.	2 yr.	Inadeq.	2 yr.	+	+	—	—	—	—	3.0	2/45	0	——
Pe	F	W	48	46	A. N. S.	2 yr.	Adeq.	3 yr.	+	—	—	+	+	+	4.0	2/46	0	Died—14 mo. (Cer. embol.)
Pi	M	W	46	46	—	26 yr.	12 Bis.	4 yr.	+	—	+	—	—	—	4.0	9/46	0	Imp.—18 mo.
Ri	M	B	44	41	M.V.	25 yr.	Inadeq.	1½ yr.	+	+	+	+	+	+	3.0	9/44	0	Imp.—36 mo.
Roq	M	B	52	52	G.P.	32 yr.	Inadeq.	—	—	—	—	—	—	—	4.0	4/45	0	Same—34 mo.
Ros	F	W	64	54	—	10 yr.	Adeq.	5 yr.	+	—	—	—	—	—	5.0	12/47	0	——
Se	M	W	53	53	G.P.	Adm.	0	—	—	—	—	—	—	—	7.2 P. O. B.	12/46	0	Same—14 mo.
Sp	M	W	52	50	T.D.	8 yr.	Inadeq.	2 yr.	+	+	+	—	+	—	3.5 4.2 P. O. B.	2/46 2/48	0	Worse—24 mo.
Vic	M	B	54	54	—	5 yr.	Inadeq.	2 mo.	+	—	+	—	—	—	4.0	1/48	0	——
Vid	M	W	52	52	A. N. S.	25 yr.	15 Bis.	3 yr.	+	—	—	—	—	—	5.3	5/47	0	Imp.—9 mo.
Wa	M	W	53	53	—	1 yr.	9 Bis.	2 yr.	+	+	—	+	+	+	9.0 P. O. B.	1/48	0	——
Wi	F	B	35	35	M.V.	2 yr.	0	1 yr.	+	—	—	—	—	—	6.0	12/45	3	——
Ye	M	Y	62	62	T.D.	Adm.	Few Bis.	—	—	—	—	—	—	—	3.0	4/45	0	Same—44 mo.
Fe	M	W	62	62	G.P.	1 yr.	9.0 POB	—	—	—	—	—	—	—	30.0	1/48	0	——
Hol	M	B	47	46	—	27 yr.	Inadeq.	—	—	—	—	—	—	—	4.0	11/46	0	Same—14 mo.

*C.N.S., central nervous system.
A.N.S., asymptomatic neurosyphilis.
M.V., meningovascular syphilis.
T.D., tabes dorsalis.
T.P., taboparesis.
G.P., general paresis.
P.R., Puerto Rican:
P.O.B., Penicillin in oil and beeswax.
†Improved.
‡Congestive heart failure.

this reason, we employed three injections of 0.2 Gm. of bismuth subsalicylate in oil, five days apart, before starting penicillin. For a variety of reasons, however, not all patients received this preliminary treatment.

MATERIAL STUDIED

The material in this report consists of the study of thirty-nine patients with cardiovascular syphilis. Thirty had aortic insufficiency and nine had saccular aneurysm or aneurysmal dilatation of the aorta.

An additional twenty-two patients in whom syphilis of the cardiovascular system was suspected have been treated with penicillin. Eighteen of these patients, all of whom had been admitted for treatment of neurosyphilis, were diagnosed as having uncomplicated aortitis. Four had aortic insufficiency and serologic findings indicative of syphilis, but rheumatic fever could not be excluded as the etiological factor in the cardiac involvement. These twenty-two patients are not included in this study, but it may be stated that no untoward reactions were observed in this group after the institution of penicillin therapy.

OBSERVATIONS

Aortic Insufficiency.—The age, sex, and color distribution of the thirty patients with syphilitic aortic insufficiency are summarized in Table I.

In addition to aortic insufficiency, eight patients also had aneurysmal dilatation of the aorta, one had saccular aneurysms of the arch of the aorta and of the innominate artery, and four were suspected of having coronary ostial stenosis. Twenty of the thirty patients gave a history of diminished cardiac reserve for periods of one month to five years prior to admission, and nine had had at least one bout of congestive heart failure.

Eight of the thirty patients had had no previous antisyphilitic treatment; only three of the remaining twenty-two had had as many as twenty injections of bismuth and twenty of arsenical drugs.

Treatment: Three of the eight patients who had had no previous antisyphilitic therapy received no preliminary treatment with bismuth. Four of the remainder received three injections of 0.2 Gm. of bismuth subsalicylate in oil, and one received only two bismuth injections before penicillin was started.

The twenty-two patients who had had some previous antisyphilitic treatment were not given preliminary bismuth, although some had received no antisyphilitic therapy for several years.

Penicillin was given in full dosage from the start of treatment (30,000 to 50,000 units every three hours). Total dosage was 3 to 6 million units. Three patients received penicillin in oil and beeswax (300,000 to 600,000 units daily), totaling 4.2, 7.2, and 9.0 million units, respectively.

Results: There were no untoward reactions attributable to penicillin therapy in any of these patients. Three presented cardiac symptoms during treatment. One of the three had been admitted in congestive heart failure with a history of precordial pain and paroxysmal dyspnea, and he had had two bouts

P.O.B., Penicillin in oil and beeswax.
†Improved.
‡Congestive heart failure.

G.P., general paresis.

M.V., meningovascular syphilis.

of heart failure in the year prior to admission. After treatment for congestive heart failure, penicillin was started without preliminary bismuth. During the first week of treatment the patient experienced several bouts of precordial pain no different from his previous attacks; during the second week of penicillin he experienced no untoward symptoms. He died in his fourth bout of congestive heart failure two months after the completion of penicillin treatment. The second of these patients was admitted in congestive heart failure with a history of precordial pain and paroxysmal dyspnea for an undetermined period before admission. She did not respond to the usual measures for congestive heart failure, and penicillin was started after she had received three injections of bismuth. She remained in congestive heart failure and died five weeks after penicillin therapy. Neither of these patients had had previous antisyphilitic therapy. It was considered that the natural course of the disease prevailed in these two patients.

A third patient gave a history of diminished cardiac reserve for two years prior to admission. He had had "several" bouts of congestive heart failure during this time, with precordial pain and nocturnal paroxysmal dyspnea, and had been on digitalis for one year. He experienced symptoms during penicillin therapy similar to his previous attacks. When seen two months after treatment, he stated that he had not had nocturnal paroxysmal dyspnea, and he was fairly well compensated.

There were no untoward symptoms during or after penicillin therapy in the remaining twenty-seven patients.

Aneurysm.—Four patients with saccular aneurysm and five with diffuse aneurysmal dilatation of the aorta were treated with penicillin (Table II).

TABLE II. SACCULAR ANEURYSM AND ANEURYSMAL DILATATION

PATIENT	SEX	COLOR	AGE ON ADMISSION	AGE AT C-V DIAGNOSIS	C-V DIAGNOSIS	C.N.S. DIAGNOSIS	KNOWN DURATION OF SYPHILIS (YEARS)	PREVIOUS ANTISYPHILITIC TREATMENT	C-V SYMPTOMS	PENICILLIN	DATE	PRELIMINARY BISMUTH
Br	M	W	55	55	A.D.	T.D.	36	Adequate	0	3.4	6/46	0
Ea	M	B	47	47	A.D.	T.D.	Admission	0	0	6.0	3/46	0
Fr	M	W	51	50	S.A.	T.D.	31	Inadequate	+	6.0	2/47	2
Ga	M	W	71	71	Multiple S.A.	M.V.	Admission	0	0	9.0POB	12/47	0
Jo	M	B	43	43	A.D.	T.P.	31	Adequate	0	6.0	9/45	0
Na	M	W	50	50	A.D.	A.N.S.	20	Adequate	0	2.0	4/45	0
No	M	W	63	61	S.A.	0	Unknown	Inadequate	0	4.0	5/47	0
Po	M	Y	53	53	A.D.	T.D.	Unknown	Inadequate	0	6.0	9/45	0
										6.0	7/46	
Sz	F	W	46	46	S.A.	M.V.	18	0	0	6.0	3/47	0

C-V, cardiovascular.
A.D., aneurysmal dilatation of aorta.
S.A., saccular aneurysm of aorta.
†C.N.S., central nervous system.
T.D., tabes dorsalis.
M.V., meningovascular syphilis.
A.N.S., asymptomatic neurosyphilis.
T.P., taboparesis.
P.O.B., penicillin in oil and beeswax.

Only one patient had symptoms referable to the aneurysm. In this patient, pressure on the left main bronchus had produced secondary pulmonary changes, and he has since died.

Three patients had had large amounts of previous antisyphilitic treatment with heavy metals and arsenical drugs. Three had had no previous treatment; they did not receive preliminary treatment with bismuth. No reaction of any kind was noted in the penicillin treatment of these patients. With the exception of the one patient who died, all were asymptomatic when last seen.

DISCUSSION

In the syphilis clinic at Bellevue Hospital we have long believed that the gloomy prognosis of syphilitic aortic insufficiency, frequently found in the literature, was not justifiable. The report of Reader and coauthors[8] offers evidence that the prognosis of this disease is better than was previously believed, and that this holds true not only for patients without diminished cardiac reserve but also for the symptomatic group. Our own expericnce has been similar to that reported from New York Hospital. For this reason, we believe that every patient with cardiovascular syphilis should be treated, if he has not previously had adequate antisyphilitic therapy.

We believe that until much larger series of patients have been observed, it is wise to use preliminary bismuth medication before starting penicillin. The use of small doses of penicillin to avoid Herxheimer reactions, as originally suggested by Moore,[2] is no longer advised. Moore has pointed out that it is now difficult to define a "small dose" of penicillin, in view of the report of Tucker and Farmer[4] that febrile Herxheimer reactions occurred during the treatment of late syphilis after doses of penicillin as small as 500 units.

Differential Diagnosis.—The difficulty occasionally encountered in making a differential diagnosis between syphilis and rheumatic fever as the etiological agent of aortic insufficiency is brought out well by one patient previously mentioned.

This 48-year-old white woman had had five bouts of congestive heart failure in the three years prior to admission to this service. She had been carried on one of the medical services as a rheumatic cardiac with mitral insufficiency and stenosis, and aortic insufficiency. A positive serologic test for syphilis was discovered two and one-half years earlier, and she had received eighteen injections of an arsenical and eighteen of bismuth up to one year before admission to this service. Because of positive spinal fluid findings for syphilis she was transferred to us for antisyphilitic therapy. She received 4 million units of penicillin in aqueous solution.

Following penicillin therapy, marked diminution of cardiac reserve continued, and subsequently the patient was twice admitted to the medical service in congestive heart failure. Fourteen months after treatment she was admitted in coma with a right hemiplegia. The cardiac rhythm was auricular fibrillation. It was believed that her course had been typical of rheumatic heart disease with the terminal episode due to cerebral embolization from left-sided mural thrombi.

Necropsy revealed that she had syphilitic aortitis with stenosis of the coronary ostia and syphilis of the aortic valve with insufficiency. The mitral valve was normal. There were thrombi in both auricular appendages and infarcts in the brain, lungs, spleen, and kidneys.

Clinical Improvement Following Penicillin Therapy.—As seen in Table I, seven of the patients with aortic insufficiency "claim to be improved" after treatment. Table I shows that of these seven patients, one denied symptoms of diminished cardiac reserve on admission but later said he had had dyspnea on exertion; three described dyspnea on exertion (one with precordial pain); one described dyspnea on exertion and nocturnal paroxysmal dyspnea; and two had been in congestive heart failure, with histories of precordial pain and nocturnal paroxysmal dyspnea. The last two patients were on digitalis at the time of treatment and have continued it since. All seven patients are working at present, and claim to be able to do more work with less discomfort than formerly. Adequate antisyphilitic therapy is expected to arrest a syphilitic inflammatory process in the aorta, but it is difficult to attribute an increase in cardiac reserve to the arrest of such a process. We believe that the apparent improvement in cardiac reserve noted by these patients is due to a general systemic improvement following the eradication of the chronic low-grade syphilitic infection.

CONCLUSIONS

1. Thirty-nine patients with cardiovascular syphilis (thirty with aortic insufficiency and nine with saccular aneurysm or aneurysmal dilatation of the aorta) were treated with penicillin in full dosage from the start of treatment.
2. No untoward reactions attributable to penicillin were observed.
3. It is believed that the danger of Herxheimer reactions has been overemphasized, but until much larger series of patients have been observed, it is advisable to administer bismuth before starting penicillin in patients who have received no previous antisyphilitic therapy.

ADDENDUM

To May, 1949, fifty patients with aortic insufficiency and ten patients with aneurysm were treated with penicillin. There were no adverse reactions encountered in this group.

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MITRAL STENOSIS: AN EXPERIMENTAL STUDY OF PULMONARY-AZYGOS VENOUS ANASTOMOSIS

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IN RECENT years attention has been directed toward surgical procedures designed to improve or restore to normal the pathologic physiology resulting from congenital or acquired defects in the cardiovascular system. Several very valuable operations have been evolved, most of which, such as the ligation of patent ductus arteriosus as devised by Gross[1] and the arterial shunt in pulmonary stenosis as devised by Blalock and Taussig[2] and modified by Potts and co-workers,[3] are aimed primarily at alterations of blood flow on the arterial side of the vascular tree. The long history of the operative repair of arteriovenous aneurysms has been that of a steady increase in understanding and improvements in the operative repair of a physiologic abnormality in blood flow. At least one procedure on the arterial side, however, is aimed to alter not primarily blood flow, but to relieve intravascular pressure. This consists of the repair of coarctation of the aorta as devised independently by Craaford[4] and by Gross.[5] The primary merit of this procedure is that the operation removes the cause of the abnormal physiology and restores the circulatory system to the normal status, and thus aborts the ill affects on other organs which develop secondarily. On the venous side of the systemic circulation, the portocaval and lienorenal shunt procedure, as advocated by Blakemore and Lord,[6] is likewise devised to reduce abnormal intravascular pressure. This procedure is still in the early stages of evaluation, and is unlike the repair of coarctation in that the primary cause of hypertension is not removed. The operation is akin to an escape valve to allow release of pressure by virtue of flow through the new channel.

A very similar type of operation on the venous side of the pulmonary circuit has been devised for potential use in conditions in which there is hypertension in the pulmonary veins. Of these conditions, mitral stenosis is by far the outstanding clinical example. It is the purpose of this paper to outline the experimental observations which have been made relative to the making of such a pulmonocaval venous shunt.

The exact pathogenesis of right-sided heart failure following stenosis of the mitral valve has never been established by adequate experimental or clinical data. Most of the evidence is indirect, but it is of such a compelling nature that there exists a general consensus as to the mechanism of this phenomenon.

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It is thought that by virtue of the narrowing of the valve, blood flow through it is impeded. Blood dammed back into the left auricle and venous pulmonary system increases the pressure within that system. With the increase in pressure, flow through the valve is augmented, but gradual dilatation of the left auricle occurs, and the pressure within the system over a period of time continues to mount. This pressure is transmitted throughout the capillary system on to the arterial side of the pulmonary tree. With this increased resistance, pulmonary arterial pressure rises, and the work of the right heart is correspondingly increased. Changes in the pulmonary arterioles and capillaries accompany this increase in pressure. Although the output of the right heart is not materially increased, its work load is augmented because of this phenomenon of pressure. The right side hypertrophies under these conditions and gradually comes to failure.

This theory is substantiated by many clinical observations: the dilatation of the left auricle, the prominence of the pulmonary vascular tree, the frequent occurrence of pulmonary hemorrhage, the loud snapping sound of the pulmonary valve, and, finally, the enlargement of the right ventricle and eventual failure. It is to be observed that the underlying physiologic abnormality on which this chain of events is predicated is an increase of pressure in the pulmonary venous tree. This concept, however, has not been substantiated by actual direct measurements either in man or in animals. The technical difficulty of creating experimental mitral stenosis has proved a severe stumbling block in the study of this condition. Until the advent of the cardiac catheter, measurement of the pulmonary artery pressure in man was unobtainable. Since that time a paucity of measurements of the pulmonary artery pressure in patients with mitral stenosis have been published in the literature. Direct measurement of the pulmonary venous pressures in man is still unobtainable. However, in spite of this lack of direct confirmatory data, because of the strong circumstantial evidence, the pressure mechanism of the pathogenesis of right ventricular failure in mitral stenosis has become widely accepted.

If this mechanism exists, it might be desirable to attempt to reduce the venous pressure in the pulmonary circuit in an effort to forestall or prevent the subsequent chain of events leading to cardiac failure. It is technically feasible to create a venous shunt between the pulmonary vein and the superior vena cava. The technique for accomplishing this in experimental animals is herein described.

However, it is not at all certain that this procedure would necessarily be of value in patients with obstruction of the mitral valve. The extent to which blood flow through the stenosed valve is dependent on the venous pressure (left atrium and pulmonary veins) is not known. It is entirely conceivable that reduction of this pressure may significantly diminish flow through the valve and thus seriously jeopardize the output of the left ventricle. It is also clear that whatever blood flows from this shunt must immediately enter the right auricle and again be sent through the right ventricle to the lungs. There will thus be a "circus movement" of blood which repeatedly traverses the right

ventricle, and the output of this side of the heart must increase to maintain the output of the left ventricle (Fig. 1). Whether in the long run this increase in output, which presumably would occur at a normal pressure level as far as the right ventricle is concerned, would be less injurious to the right ventricle than a smaller output at a higher pressure level is not as yet known. Accordingly, the theoretical merit of this procedure is open to serious question and must be the subject of further evaluation.

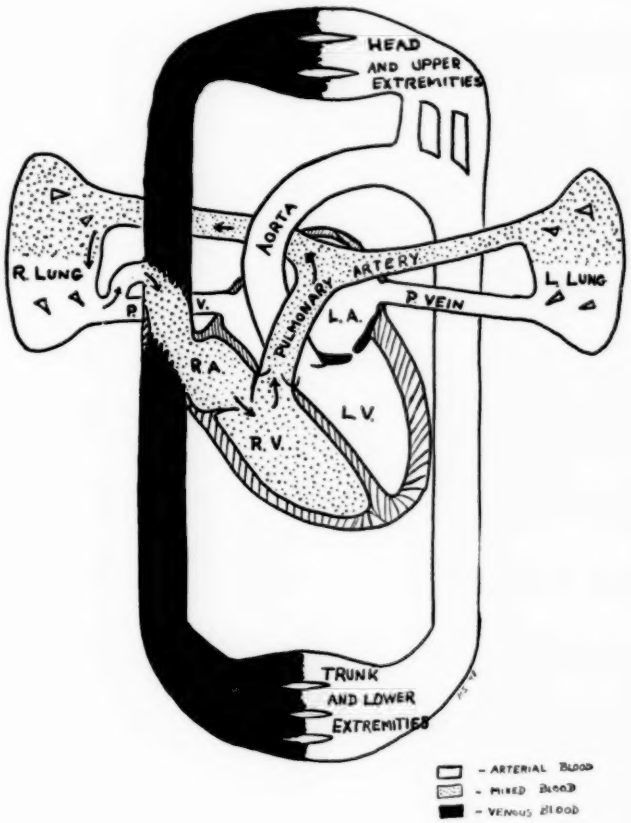

Fig. 1.—Diagram of circulation in mitral stenosis after creation of pulmonary-azygos venous shunt. Arrows show path taken by blood recirculating through right ventricle.

EXPERIMENTAL PROCEDURES

At first approach to this problem it seemed that there were three possibilities of effecting a left-to-right venous shunt. The first would most obviously be an interauricular septal defect. Second, an orifice could be made between the right pulmonary vein and the right auricle. And third, an anastomosis could be made between a pulmonary vein and a systemic vein. An interauricu-

lar septal defect can be made without too much difficulty in the experimental animal. This procedure, however, is subject to some risk, and the size of the orifice cannot always be thoroughly controlled. Moreover, intra-auricular thrombosis occasionally occurs. In the second instance, a side-to-side anastomosis of the pulmonary vein to the right auricle was subject to the same criticism, although an end-to-side return of the pulmonary vein to the right auricle is technically quite feasible. The most likely possibility appeared to be, therefore, the use of a systemic vein with anastomosis to the pulmonary vein, and the most obvious vein available for this purpose was the azygos vein, because of its relatively large size and its proximity to the right pulmonary vein as it arches over to the root of the right lung. This method was therefore adopted for study.

The first attempt was to make a suture anastomosis between the proximal end of the divided azygos vein and the side of the exposed right pulmonary vein (Fig. 2,*B*). This maneuver was found to be fraught with considerable technical difficulties because of the friable nature of the wall of the pulmonary vein in dogs. Even when this procedure was successfully performed, however, in the normal animal there was uniform occlusion of the opening from thrombosis at the site of anastomosis. This was not surprising, and demonstrated the well-known difficulty encountered in venous anastomosis when there is no pressure gradient between the two ends of the shunt. Frequent measurements of the pressures within the pulmonary vein and the vena cava in the normal dog (open chest) revealed that there is seldom more than 3.0, and never more than 5.0 cm. of water difference between the two systems.

A similar fate was met with the Vitallium tube technique when an end-to-side anastomosis was made (Fig. 2,*C*). Here the difficulty was slightly different in nature. If a tube of adequate size (5.0 to 8.0 mm. in diameter) was inserted into the side of the pulmonary vein, enough puckering occurred with the insertion of the encircling ligatures to force the tube well into its lumen and into the orifice where the right pulmonary vein enters the left auricle. This materially obstructed the flow of blood through the vein and thrombosis within the tube likewise still occurred. Because of the mechanical obstruction by this method, it was felt that except in the presence of a considerably dilated pulmonary vein, this threat to pulmonary venous flow was such as to make an end-to-side tube anastomosis a procedure of doubtful merit.

Accordingly, effort was directed toward constructing an end-to-end anastomosis between the proximal end of the ligated azygos vein and the proximal end of the divided branch of the pulmonary vein which led from the right upper lobe of the lung (Fig. 2,*D* and *E*). In most animals these structures are of approximately the same size. It was not perfectly clear, from the available literature, what would be the fate of the upper lobe of the lung when its vein was ligated and divided. This problem, therefore, was studied experimentally and the result has been previously published.[7] Although there is an immediate intense engorgement of the pulmonary parenchyma and the alveolar spaces, there occurred no necrosis of the pulmonary tissue, and after a period of about four months,

with the resorption of the hemorrhagic exudate and formation of venous collateral, the pulmonary tissue returned almost, although not quite to normal.

Since there was very little pressure gradient existing in the animal between the pressures in the superior pulmonary vein and vena cava, the value of

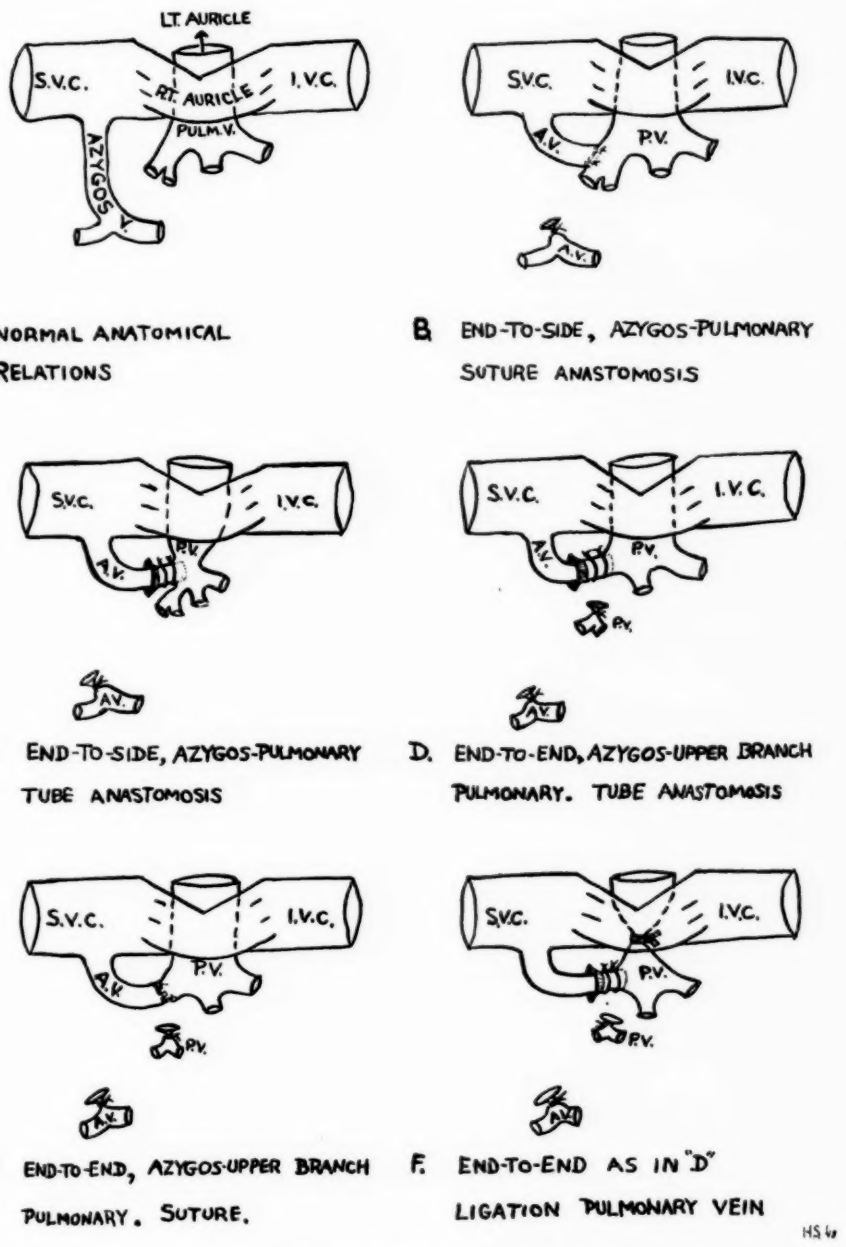

Fig. 2.—Diagrammatic illustrations of various experimental procedures. Plan "D" is the method of choice in experimental animals.

dicoumarin in preventing venous thrombosis within the anastomosis was examined. In the dog, dicoumarin is a treacherous drug, since the response is quite variable from animal to animal, and the margin of safety in terms of dosage in any one animal is small. It was difficult to obtain a steady elevation in prothrombin time, or to correlate the prothrombin time to the bleeding tendency. In many animals in which where was an elevation of only three to four seconds over the normal (nineteen seconds in normal animals, using whole blood with Difco's thromboplastin), a marked bleeding tendency was apparent. In every animal on which operation was performed and in which the prothrombin time had been increased, death occurred from hemorrhage, although in one animal the operation had proceeded no further than rib resection.

Fig. 3.—Photograph of specimen from Dog 48-24. Probe handle passes easily through the shunt.

A technique of giving the animal dicoumarin approximately eighteen hours before operation was therefore devised. At the time of operation, the prothrombin time was normal. Between six and twenty-four hours following operation the prothrombin times were elevated, but as has been mentioned, a persistent elevation without marked variation was not obtained. However, when use was made of an end-to-end Vitallium tube anastomosis between the proximal ends of the azygos vein and the upper lobe branch of the right pulmonary vein, accompanied by this method of dicoumarin administration, a patent anastomosis was consistently obtained (Fig. 3).

It was observed, however, that the caliber of that part of the vein which traversed the Vitallium tube was narrowed by perivascular fibrosis which oc-

curred between the tube and the vein. Thus, when a 5.0 mm. tube was used, the effective diameter of the shunt would be reduced to about 3.0 millimeters.

In order to evaluate the importance of a differential in pressure, a series of animals was done in which an end-to-end type of anastomosis was made, following which the pulmonary vein proximal to the anastomosis was either partially or completely occluded by ligature (Fig. 2,*F*). It was felt that this obstruction to the return flow of the blood in the vein to the left auricle would increase the pressure in this vein and would partially simulate the venous hypertension of mitral stenosis. This was found to be the case, and anastomoses created in this fashion remained widely patent without thrombosis or narrowing. An end-to-side suture anastomosis, however, in the presence of total pulmonary venous ligation, gradually thrombosed and was obliterated.

Table I gives a summary of the results in these experiments.

All operations were performed under strictly aseptic conditions, using intravenous barbiturate anesthesia with a mechanical respirator. Mongrel dogs of various sizes were used, although attempt was made to use larger animals weighing 10 kilograms or more. Observations were made at intervals following the anastomosis varying from three weeks to as long as four months.

The operative procedure was briefly as follows:

Exposure was obtained through an anterolateral incision in the fourth right intercostal space. The azygos vein was first dissected free, and then ligated just at the point where the first major branch from the upper intercostal veins enter. In most animals this gave a length of about two inches. A bulldog clamp was applied near the vena cava, and the vessel was cut just proximal to the ligation. A small moist pack was placed over the vein to avoid desiccation. Attention was now directed to the pulmonary vein. A few cubic centimeters of 2 per cent Novocain were injected into the pericardium to minimize the possibility of serious cardiac arrhythmias. The pericardium was grasped just above the phrenic nerve with two Allis forceps and traction exerted upward. Incision was now made between the pulmonary vein and the pericardium and dissection was carried inward, separating the pulmonary vein from the right auricle. This part of the procedure was always delicate and time consuming. The pulmonary vein was finally freed posteriorly and was thus mobilized almost to its entrance into the left auricle. The operation was now completed by making the desired type of anastomosis, and then closing the chest wall, making sure the lungs were well inflated. The animals tolerated this procedure without difficulty.

COMMENTS

The use of dicoumarin in dogs gave rise to many technical difficulties and was found to be completely unnecessary when a pressure gradient was introduced. This would parallel the situation to be expected in the clinical patient with mitral stenosis. The end-to-end type of anastomosis, with the subsequent engorgement of the upper lobe of the lung, would appear to be less desirable than an end-to-side anastomosis, at least in theory. In the presence of a dilated pulmonary vein, the end-to-side anastomosis using the tube technique

TABLE I. SUMMARY OF EXPERIMENTAL RESULTS

DOG	PROCEDURE	DATE OPERATION	DATE AUTOPSY	CALIBER OF LUMEN (MM.)	SUMMARY
		No Dicoumarin or Pressure Gradient			
46–40	End-to-side, suture, satisfactory	5–20–46	6– 4–46	0	No patent anastomosis obtained in the eight dogs surviving operation; in addition, two operative deaths from hemorrhage
46–48	End-to-side, suture, constricted	5–23–46	6–26–46	0	
46–50	End-to-end, suture, satisfactory	5–30–46	6–26–46	0	
46–58	End-to-end, tube 4 mm., satisfactory	6–21–46	8–13–46	0	
46–61	End-to-side, tube 5 mm., poor	7–15–46	8–13–46	0	
46–75	End-to-end, tube 5 mm., satisfactory	11–13–46	12–10–46	0	
47–35	End-to-end, tube 4 mm., satisfactory	8–12–47	9–10–47	0	
47–36	End-to-end, tube 6 mm., satisfactory	8–13–47	9–10–47	0	
		Dicoumarin; No Pressure Gradient			
47–3	End-to-end, tube 4 mm., satisfactory	1–31–47	2–26–47	2	A patent anastomosis was obtained in seven of nine dogs surviving three days or more; all anastomoses narrowed by perivascular fibrosis; in addition, three postoperative deaths from hemorrhage (dicoumarin)
47–4	End-to-end, tube 5 mm., satisfactory	2– 3–47	2– 5–47	5	
47–6	End-to-end, tube 5 mm., satisfactory	2–14–47	3– 4–47	1	
47–10	End-to-end, tube 4 mm., inadequate dicoumarin	3– 3–47	3–20–47	0	
47–12	End-to-end, tube 5 mm., satisfactory	3– 7–47	3–26–47	2	
47–16	End-to-end, tube 7 mm., satisfactory	3–21–47	3–26–47	6	
47–34	End-to-end, tube 6 mm., satisfactory	7–10–47	7–28–47	2	
47–36	End-to-end, tube 6 mm., satisfactory	7–15–47	8– 4–47	2	
47–40	End-to-side, tube 6 mm., poor	7–22–47	8–20–47	0	
		No Dicoumarin; Pressure Gradient (Partial Ligation of Pulmonary Vein)			
47–102	End-to-end, tube 5 mm., satisfactory	1– 9–48	1–29–48	5	All five end-to-end tube anastomoses widely patent; two end-to-side suture anastomoses became occluded; no operative or postoperative mortality
48–19	End-to-end, tube 6 mm., satisfactory	1–14–48	3–15–48	4	
48–23	End-to-end, tube 7 mm., satisfactory	1–26–48	3–15–48	3	
48–22	End-to-end, tube 5 mm., satisfactory	2– 2–48	3–15–48	4	
48–24	End-to-end, tube 6 mm., satisfactory	2–16–48	3–15–48	4	
48–28	End-to-side, suture, satisfactory	3–23–48	4–19–48	0	
47–77	End-to-side, suture, satisfactory	3–24–48	4–19–48	0	
		No Dicoumarin; Pressure Gradient (Complete Ligation Pulmonary Vein)			
48–18	End-to-end, tube 7 mm., satisfactory	1–16–48	2–16–48	6	Both procedures resulted in widely patent anastomoses; one postoperative death
47–86	End-to-end, suture, satisfactory	3–23–48	4–19–48	4	

might be quite possible. However, the potential element of partial obstruction of the flow from this vein into the left auricle must not be overlooked. In the normal animal, ligation of the branch of the pulmonary vein to the right upper lobe is well tolerated; whether this would be equally true in a patient with mitral stenosis is open to question.

SUMMARY

1. The possibility of the creation of a venous shunt between the pulmonary vein and the superior vena cava by the use of a proximal segment of the azygos vein in patients with mitral stenosis and pulmonary venous hypertension is suggested. The effect upon cardiovascular hemodynamics of such a procedure remains to be investigated.

2. That such a shunt is technically feasible in dogs by means of an end-to-end anastomosis of the azygos and pulmonary veins, using a Vitallium tube, has been demonstrated.

3. In the presence of a pressure gradient such a shunt is well tolerated in normal animals and remains widely patent.

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THE PRECORDIAL ELECTROCARDIOGRAM IN INCOMPLETE RIGHT BUNDLE BRANCH BLOCK

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INTRODUCTION

IN 1917 Rothberger and Winterberg[1] published an electrocardiographic record which depicts the gradual clearing of a defect in conduction affecting the right branch of the bundle of His. An attempt to cut this structure in the course of an experiment on a dog blocked it only temporarily. Fortunately, one of the tracings taken spanned the period during which the injured bundle gradually recovered its conductivity. The investigators recognized that the central complexes of this record represent incomplete right bundle branch block. They are transitional in form between the preceding complexes, which are characteristic of complete block, and the subsequent complexes, which are of normal outline.

Some years later, Wilson and Herrmann,[2] without being aware of this earlier work, carried out an extensive experimental investigation in which the canine dextrocardiogram and levocardiogram were superimposed in varying time relations by a number of different methods. By producing right bundle branch block and then stimulating the anterior wall of the right ventricle just after the normal excitation wave had reached the left, they were able to produce at will complexes representing a delay in right ventricular activation of any magnitude less than that which occurs in complete right bundle branch block. Such complexes are identical with those of complete right bundle branch block with regard to the parts of the QRS wave written before excitation of the right ventricle begins; that is to say, before the excitation wave spreads to muscle normally excited via the right Purkinje plexus. They are transitional between bundle branch block complexes and normal complexes with regard to the length of the QRS interval and the form of the T wave.

The present report deals with the description, classification, and interpretation of clinical electrocardiograms which are intermediate, with regard to the form of the ventricular complex, between normal tracings and those which represent complete right bundle branch block, and which display a QRS interval measuring less than 0.12 second in the limb leads. We have attempted to establish criteria for the diagnosis of incomplete right bundle branch block and to

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learn something about its incidence and its clinical significance. Incomplete left bundle branch block has not been included in our study because of the difficulty of distinguishing the electrocardiographic changes which it produces from those that accompany enlargement of the left ventricle.

MATERIAL AND METHODS

The tracings studied were selected from a group of 39,778 electrocardiograms taken over a period of fifteen years. Among these we found 1,123 instances in which a definite or tentative diagnosis of a defect in intraventricular conduction of one kind or another had been made. We then examined those patients in whom both standard limb leads and multiple precordial leads had been taken. Since precordial leads are not taken routinely in this laboratory, we also investigated the accuracy of the impressions based on the standard and unipolar limb leads, which are taken in every case. There were 150 instances in which the extremity leads suggested that incomplete right bundle branch block might be present. In thirty-seven of these the precordial leads showed no evidence of a defect in intraventricular conduction. In the remaining 113 cases, the form of the QRS complexes of the leads from the right side of the precordium supported in a greater or lesser measure the view that activation of the right ventricle was abnormally delayed.

The limb leads considered suggestive of incomplete right bundle branch block displayed a QRS interval measuring 0.08 second or more, but less than 0.12 second, and a conspicuous broad S wave in Lead I. In some instances of this kind, the mean electrical axis was deviated to the left so that the electrocardiographic pattern bore a superficial resemblance to that produced by left ventricular enlargement and by incomplete left bundle branch block. In all such instances there were invariably small Q and S waves, as well as a dominant R deflection in Lead I. The presence of both a primary and a secondary R wave in the unipolar right arm lead (Lead V_R) was thought at first to be of value in detecting cases of incomplete right bundle branch block, but further investigation did not strongly support this impression.

One hundred seventy-two cases of complete right bundle branch block diagnosed on the basis of the changes in the precordial leads, were also reviewed in order to ascertain whether the variations in electrocardiographic pattern observed in incomplete right bundle branch block are or are not similar to those that occur when the block is complete.

CLASSIFICATION

Cases of incomplete right bundle branch block associated with myocardial infarction and with pulmonary embolism will be considered separately. The basis for the classification of the rest of our material has been the configuration of the QRS group in the leads from the right side of the precordium. The groups, subgroups, and classes distinguished are listed below. A primary R and a late R′ deflection were present in one or more of Leads V_1, V_2, and V_E in all cases

except those in which a diagnosis of anterior infarction had been made, and one additional case which has been placed alone in Group VII.

Group I.—The R and R′ waves of Lead V_1 are both small and of nearly the same size. The R′ deflection does not exceed 5.0 mm. in height. If an S wave is present it is not over 5.0 mm. in depth (Fig. 7,*A*). This group contains twenty-eight cases.

Group II.—The primary and secondary R waves of Lead V_1 are separated by a deep S deflection always more and usually much more than 5.0 mm. in depth. This group contains twenty-two cases, which have been placed in two subgroups as follows:

A. The R and R′ waves are both small and of about the same voltage (Fig. 7,*B*). This subgroup contains seventeen cases.

B. The R wave is small, but R′ is between 5.0 and 10 mm. in height (Fig. 7,*C*). This subgroup contains five cases.

Group III.—The initial R wave is small and R′ is at least 6.0 and usually more than 10 mm. in height. This group contains thirty cases. On the basis of the behavior of the two R deflections as the precordial electrode was moved to the left, they were divided into the following four subgroups:

A. The R′ wave is largest in Lead V_1 or Lead V_2, becomes smaller with each successive lead, and is usually absent or inconspicuous in Lead V_3 or Lead V_4. In the leads from the left side of the precordium the R deflection is relatively small (Fig. 7,*E*). This subgroup contains eleven cases.

B. The tracings of this subgroup are similar to those of the preceding with regard to the size of the R′ wave, but there are small initial R deflections and very deep S waves in the leads from the central part of the precordium, that is, in one or more of Leads V_2 to V_5. There are large R′ waves in the leads from the extreme right side of the precordium and large R waves in the leads from the extreme left side of the precordium, but small R and deep S waves in the other precordial leads (Fig. 7,*F*). This subgroup contains eight cases.

C. The R′ deflection is conspicuous only in Lead V_1 or in Leads V_1 and V_2. The initial R wave grows rapidly with each succeeding lead and is very tall in the leads from the extreme left side of the precordium. The transitional zone, yielding complexes intermediate in form between those obtained from the extreme right side and those obtained from the extreme left side of the precordium, is unusually far to the right (Fig. 7,*G*). This subgroup contains six cases.

D. As the exploring electrode is shifted to the left, the size of the R′ decreases less rapidly than in subgroups *A*, *B*, and *C*, and is tall in the first three, four, or even five precordial leads. Instead of being replaced by an S wave in the leads from the transitional zone, it appears to approach the R deflection and become fused with it (Fig. 7,*H*). This subgroup contains six cases.

Group IV. This group includes cases of incomplete right bundle branch block associated with right ventricular hypertrophy. These are discussed in a separate section.

Group V. This group contains eleven cases of myocardial infarction.

Group VI. This group contains two cases of pulmonary embolism.

Group VII. This group contains only one case. All the precordial leads yielded complexes which are transitional in form (Fig. 9).

Our cases were also classified on the basis of the number of precordial leads showing evidence of a conduction defect suggestive of incomplete right bundle branch block, as follows:

Class a.—In forty-seven cases changes of the kind in question were present in Leads V_1, V_2, and V_E.

Class b.—In thirty-six cases there was no late R′ deflection in Lead V_E, but such a deflection was present in Leads V_1 and V_2.

Class c.—In five cases R and R′ waves were present in Leads V_1 and V_E, but there was no secondary R′ wave in Lead V_2.

Class d.—In twenty-four cases R and R′ waves were conspicuous in Lead V_1 only.

Class e.—In thirteen cases an initial and a secondary R wave were present in Lead V_1 or in Leads V_1 and V_2, but Lead V_E had not been taken. These cases were at first placed in this class. Later those cases in which R and R' waves were present in Lead V_1 only were added to Class d and those in which these deflections occurred in Lead V_2 as well were added to Class b.

TABLE I. CLASSIFICATION OF INCOMPLETE RIGHT BUNDLE BRANCH BLOCK

GROUP	a	b	c	d	TOTAL	CORRECTED TOTAL	PROBABLE CASES
I	14	9	1	4	28	27	1
II	9	7	3	3	22	20	2
III	3	4	0	12	19	11	8
IV, A	7	3	0	1	11	10	1
IV, B	2	5	0	1	8	7	1
IV, C	5	1	0	0	6	6	0
IV, D	2	3	0	0	5	5	0
V	4	4	0	3	11	8	3
VI	1	0	1	0	2	2	0
VII	—	—	—	—	1	1	0
			Total		113	97	16

Table I shows the distribution with respect to classes of the cases placed in each of the groups or subgroups. The column headed "Total" gives the sum of the numbers which appear on the same horizontal line in the four preceding columns. The column headed "Corrected Total" gives the sum of the figures lying on the same horizontal line and in the columns headed "a," "b," and "c," plus a number representing cases placed in Class d, in which the evidence pointing to incomplete right bundle branch block exhibited by the standard precordial leads was supported by data furnished by unipolar leads from points to the right

of the right sternal margin, or by other records depicting complete right bundle branch block in the same patient. The column headed "Probable Cases" gives the difference between the figure in the sixth column and that in the seventh.

There were nineteen cases in which the records taken disclosed a variation in the grade of the defect in conduction. In four instances both complete and incomplete right bundle branch block were recorded. In the remainder, which are not included in our series of cases of incomplete right bundle branch block, partial or transient complete right bundle branch block was observed.

CASES SHOWING VARIATIONS IN THE GRADE OF THE CONDUCTION DEFECT

The least questionable cases of incomplete right bundle branch block are those in which complexes typical of complete right bundle branch block and complexes transitional in form between these and complexes of normal outline occur either in the same record or in the same set of records. For this reason, we have selected two cases of this kind for discussion. In order to bring out more

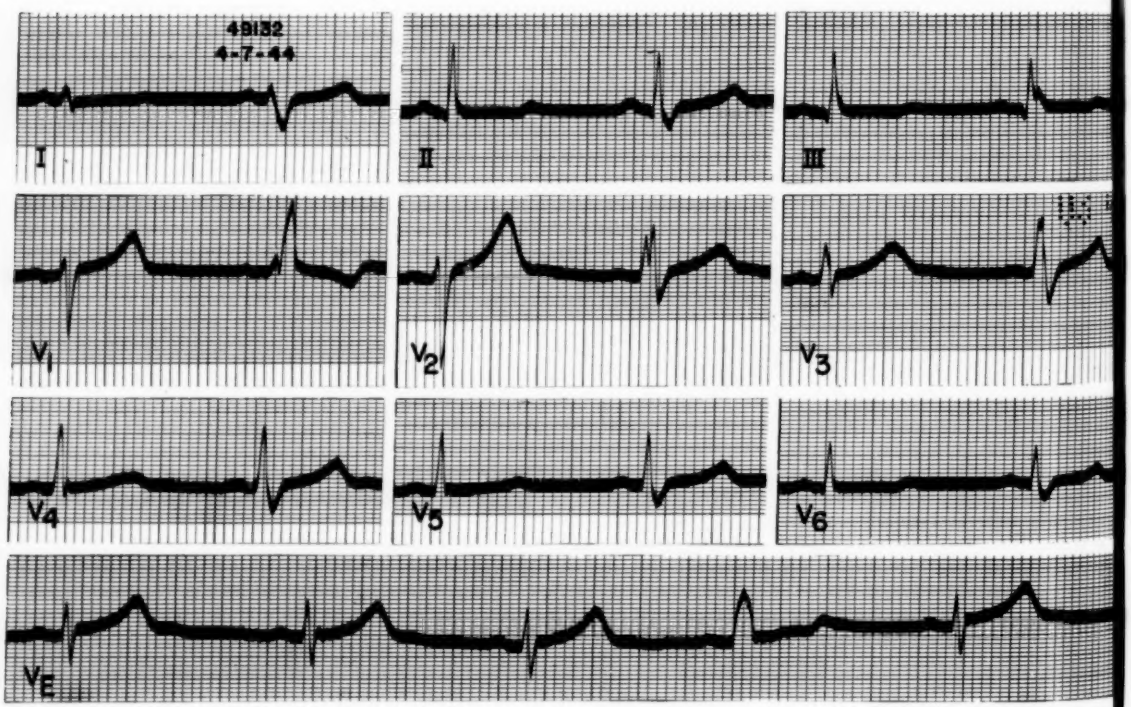

Fig. 1.—Partial right bundle branch block. The first complex of each pair represents normal intraventricular conduction; the second, complete right bundle branch block. (Reproduced with the permission of Interscience Publishers, Inc.)

clearly the similarities and differences between the two types of complexes, we have in some instances superimposed them photographically by the following procedure:

The film negative of the original electrocardiogram was printed as a positive on another strip of film. Both the negative and the positive were then put in a photographic enlarger, and a complex representing complete right bundle branch block was superimposed, in the proper time relation, upon one representing incomplete right bundle branch block, or, in one instance, normal intraventricular conduction. This was done by shifting the two complexes until the P waves and the earliest QRS components coincided, while keeping the two sets of time lines, the two sets of horizontal lines, and the two isoelectric levels parallel. The enlarged photograph made in this way shows a white and a black tracing, one upon the other, with white grid lines belonging to the first and black grid lines belonging to the second. Where black and white deflections or lines coincide the resulting tone is gray.

For purposes of comparison and orientation, we shall present first a case of partial right bundle branch block in which complexes typical of complete right bundle branch block and complexes of normal contour occurred in the same record.

The patient, a man 40 years of age, was found to have a defect in intraventricular conduction when an electrocardiogram was taken elsewhere, on Sept. 8, 1941, in the course of a routine examination. At a later date, May 24, 1943, another tracing showed normal intraventricular conduction; but on Dec. 17, 1943, right bundle branch block was again present. There were no complaints referable to the heart, and the physical examination was entirely negative. The electrocardiogram taken on April 7, 1944, at the University Hospital shows in all leads a succession of ventricular complexes typical of complete right bundle branch block, alternating with runs of complexes of normal outline. In Fig. 1 the first complex of each pair is normal and the second depicts the block. The QRS interval of the former measures 0.08 second and that of the latter, 0.12 second.

There is a striking similarity between the initial deflections of the two types of complexes in the limb leads and in precordial Leads V_1, V_4, V_5, and V_6. There is a vast difference, however, between the later QRS components, and this is most pronounced in the leads from the right side of the precordium. When right bundle branch block is present, there is in Lead V_1 a small primary R wave followed by a small downward movement which does not cross the base line, and this in turn is succeeded by a very tall secondary R wave. The normal QRS complex displays a small initial R deflection and a deep S deflection. Both types of complexes undergo the expected transformations in the successive leads of the precordial series.

The paired complexes of Lead V_1 are superimposed in Fig. 2. The white tracing represents complete right bundle branch block and the black one, normal

conduction. The initial deflections of the two complexes are nearly identical in form. The tracings diverge at a point on the descending limb of the initial R wave of the abnormal complex.

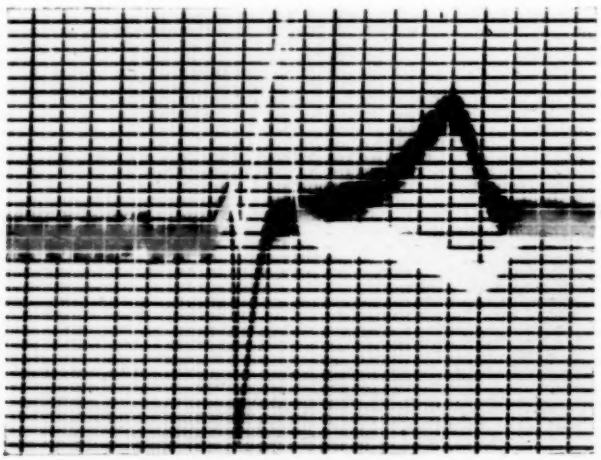

Fig. 2.—The paired complexes of Lead V_1 (Fig. 1) are superimposed.

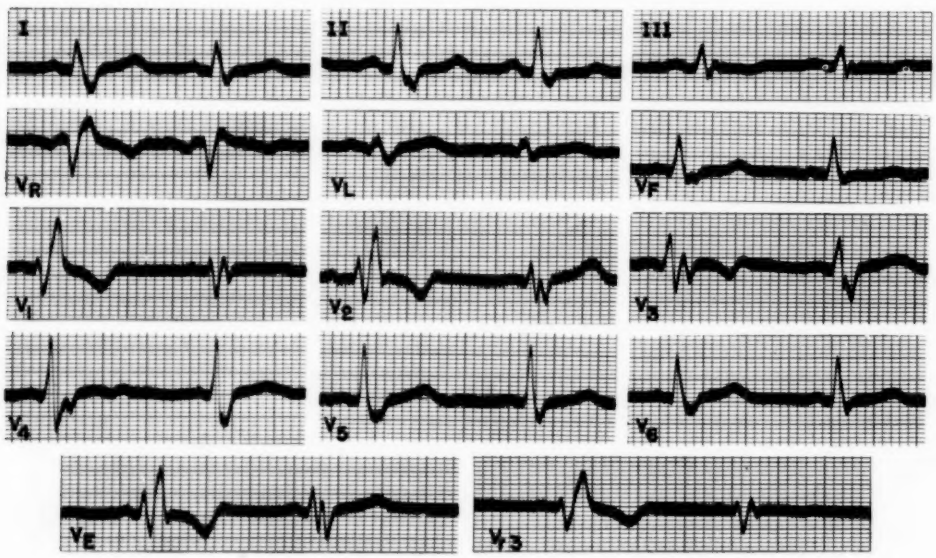

Fig. 3.—The first complex of each pair represents complete, the second incomplete right bundle branch block.

The electrocardiogram reproduced in Fig. 3 is that of a 65-year-old man who was admitted to the University Hospital on Feb. 5, 1941, for the repair of bilateral inguinal hernias. There was a history suggestive of nocturnal dyspnea, but no other complaints referable to the heart were elicited. On physical examination the cardiac border extended 10 cm. to the left of the midline. There were no murmurs, but a presystolic gallop rhythm was heard. The blood pres-

sure was 150/80. Aside from moderate peripheral arteriosclerosis, there were no abnormalities of the cardiovascular system.

The electrocardiogram taken on Feb. 18, 1941, shows complete, alternating with incomplete, right bundle branch block. In Lead I, the first complex, which represents complete block, displays broad W-shaped QRS complexes with a duration of 0.14 second. The QRS complex of the second complex measures only 0.10 second. The initial parts of the paired complexes appeared to be identical in all leads. In the limb leads and in the leads from the left side of the precordium (V_5 and V_6), they differ chiefly with respect to the width of the QRS group and the size of the T deflection. In the leads from the right side of the precordium (V_1, V_2, and V_E) and from the right fourth intercostal space in the midclavicular line (V_{R3}), the difference between them is much more pronounced.

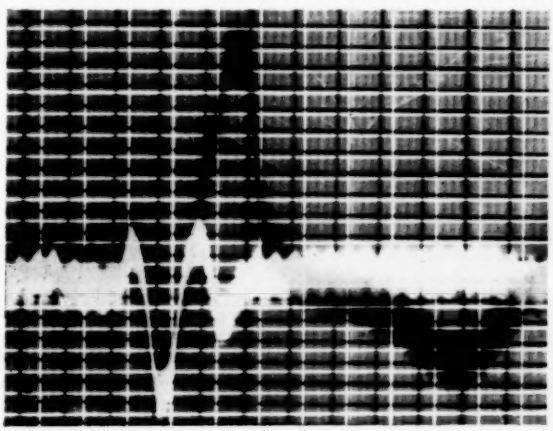

Fig. 4.—The paired complexes of Lead V_1 (Fig. 3) are superimposed.

Note that the R′ deflections are much taller in the complexes that represent complete, than in those that represent incomplete right bundle branch block. In Leads V_1 and V_{R3} the R′ deflection of the latter is approximately equal to the R wave in height; in Lead V_2 it is smaller than the R wave; and in Lead V_E it is embryonic. There is an orderly sequence of changes affecting the primary and secondary R waves of both complexes corresponding to the step-by-step movement of the exploring electrode from the right to the left side of the precordium as the successive leads were taken. The primary R wave grows taller and finally becomes the early R wave of the leads from the extreme left side of the precordium, whereas the second R deflection becomes gradually smaller and is eventually transformed into an S wave.

It is evident that except for the height of the secondary R deflection the QRS complexes of shorter duration closely resemble in general outline and behavior those which are characteristic of complete right bundle branch block. There can be little doubt that the former represent incomplete right bundle branch block. These complexes are typical of those recorded in the cases which we have placed in Group I, Class a (Fig. 7,*A*). In Fig. 4 the paired complexes

of Lead V_1 are superimposed. It will be noted that the primary R waves and the downstrokes of the S waves coincide. The divergence begins near the peak of the R′ deflection of the complex of shorter duration.

The electrocardiograms reproduced in Figs. 5 and 6 are those of a 59-year-old man who was well until Aug. 23, 1945, when he had a prolonged attack of anginal pain followed by unconsciousness for two hours, and right hemiplegia which persisted for twenty-four hours. Dyspnea and palpitation continued through the following two weeks, at the end of which time the patient was admitted to the University Hospital. Examination revealed moderate cyanosis, a heart rate of 140 per minute with regular rhythm, a blood pressure of 128/80, and a greatly enlarged heart. A Grade 1 blowing systolic murmur was audible in the pulmonic area.

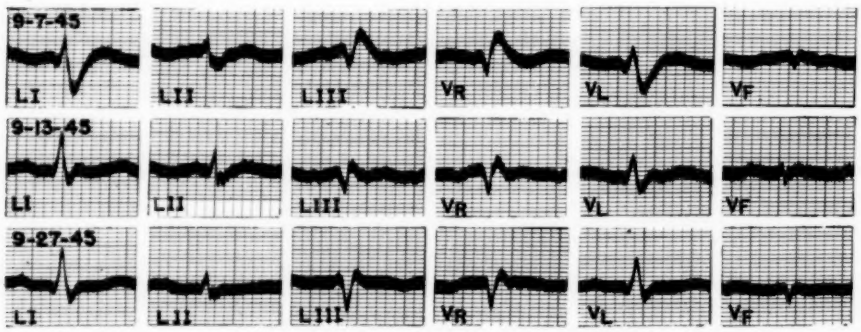

Fig. 5.—Different grades of right bundle branch block in the tracings of a 59-year-old man, who had a prolonged attack of anginal pain followed by transient hemiplegia, cardiac failure, and auricular flutter.

The electrocardiogram taken on Sept. 7, 1945, showed complete right bundle branch block. No distinct P waves were visible in the standard limb leads, but small continuous oscillations, occurring at a rate of 272 per minute, in the leads from the right side of the precordium disclosed the presence of auricular flutter with 2:1 A-V block. In the precordial leads (Fig. 6) the transitional zone is shifted somewhat to the left; compare the complexes of Lead V_4 in this record with those of Lead V_1 in Fig. 8, in which the transitional zone is well to the right. Leads from the left side of the precordium (V_5 and V_6) show early R waves and broad S deflections.

The complexes of the records of Sept. 13, 1945, are similar in outline, but the QRS interval varies considerably in duration. The heart rate is 100 per minute and the grade of A-V block is variable. The QRS complexes change in shape with the length of the preceding diastole. Thus, when the block is 2:1 the QRS interval measures 0.14 second, and when 4:1 block is present this interval measures 0.12 second. In the record taken on Sept. 27, 1945, there is normal sinus rhythm with a heart rate of 94 per minute, and the QRS interval measures 0.11 second. The only other evidence of a conduction defect in the precordial leads of this date is the presence of both an early and a late R deflec-

tion in Lead V_1. The significance of an R′ deflection in Lead V_1 alone, in cases in which there is no other evidence of heart disease, is often open to question. Certainly, in the present instance, this phenomenon appears to represent the residuum of the previously complete right bundle branch block, and therefore a minor grade of incomplete right bundle branch block.

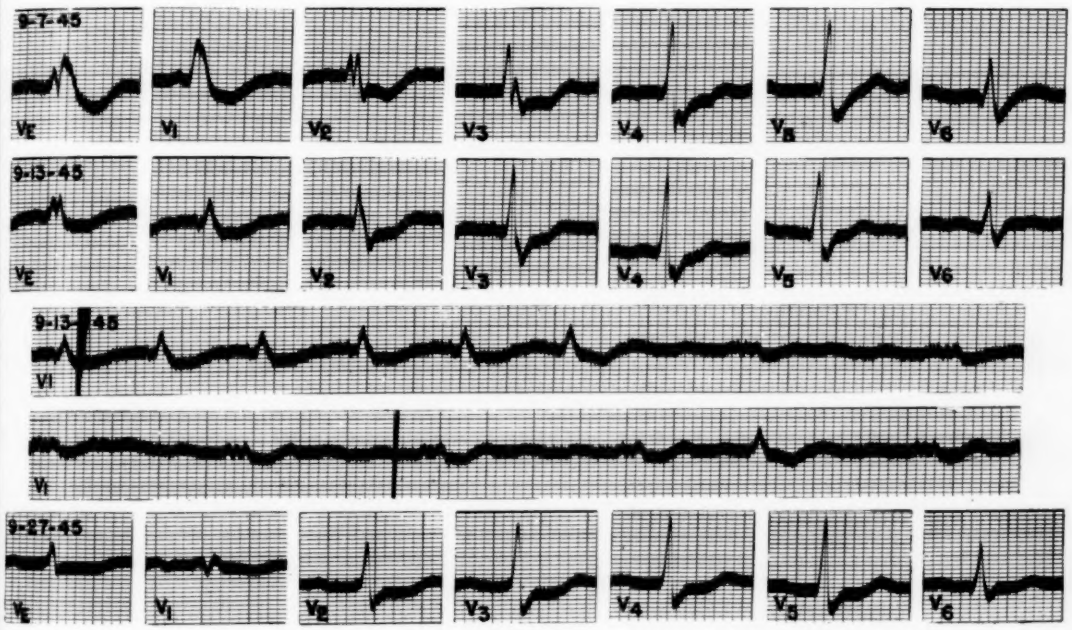

Fig. 6.—The precordial leads corresponding to the limb leads of Fig. 5.

DEFINITION OF INCOMPLETE RIGHT BUNDLE BRANCH BLOCK AND THE ORIGIN OF THE QRS DEFLECTIONS IN LEADS FROM THE RIGHT SIDE OF THE PRECORDIUM

The concept of incomplete bundle branch block is based on an analogy. Between complete and permanent A-V block, on the one hand, and slight prolongation of the P-R interval, on the other, there are many conduction defects of intermediate grade. Similar variations in the effects of disease upon the spread of the excitatory process through the bundle branches, which have a structure not unlike that of the main stem of the bundle of His, are to be expected. Complete bundle branch block is now known to be fairly common, and partial bundle branch block, in which normal intraventricular conduction alternates with complete bundle branch block, is by no means rare. The term incomplete bundle branch block is used to designate a delay in the activation of one ventricle due to a defect which slows, but does not interrupt, the transmission of the impulse through the main stem of the bundle branch which supplies this chamber. This

delay cannot exceed that which would be produced by complete block in the same case, but from a theoretical standpoint it may have any lesser magnitude. Practically, it must be great enough to be detectable by the methods available. The term incomplete bundle branch block as defined here excludes defects in conduction affecting the transmission of impulses through some subdivision of a bundle branch but not through the bundle branch as a whole.

Defects in conduction affecting the right branch of the bundle of His cannot alter the time or sequence of the excitation of the muscle normally supplied by the left branch. The electrical forces produced by the activation of this fraction of the myocardium are, therefore, in all respects the same when such defects are present as when they are absent. When there is a delay in the activation of the right ventricle, as much of the QRS complex as is written before excitation of this chamber begins is pure levocardiogram. The earliest part of the QRS complex has the same form in incomplete as in complete right bundle branch block; in both cases, it is of left ventricular origin. Theoretically, it should, then, always be possible when QRS complexes typical of complete right bundle branch block and QRS complexes of shorter duration occur in the same tracing, or same set of tracings, to ascertain whether the latter do, or do not, represent incomplete right bundle branch block, by comparing the initial components of the two types of complexes. In practice the comparison does not always give an entirely unequivocal answer, particularly when it is a question of deciding whether or not the less abnormal complexes depict a minor delay in the activation of all of the right ventricular muscle. The reason lies chiefly, although not solely, in the similarity between the initial QRS component of the complexes which represent complete right bundle branch block and that of those which represent normal intraventricular conduction in the same subject. This similarity is well illustrated by Figs. 1 and 2.

When the excitatory impulse reaches the ventricles by way of the bundle of His and its subdivisions, its direction of spread through each part of the ventricular walls and septum is perpendicular, or nearly perpendicular, to the endocardial surface which bounds it. Four sets of electrical surfaces are generated. Two of these, the forces produced by activation of the right half of the septum and those produced by activation of the free wall of the left ventricle, tend to make the epicardial surface of this chamber and the left side of the thorax positive, and the epicardial surface of the right ventricle and the right side of the thorax negative. The other two, the septal forces of the left ventricle and those produced by the free wall of the right, have the opposite polarity. The forces produced by the right side of the septum tend to make the cavity of the left ventricle positive and that of the right negative, and vice versa. The forces produced by the free walls tend to make both cavities negative. It is clear, therefore, that the QRS deflections always represent a balance of forces directly opposed one to the other.

It has been shown that the potential variations of any point on the precordium are closely related to those of the nearest parts of the epicardial surface.[3] The deflections of unipolar leads from the right side of the precordium are ordinarily similar in general outline and in origin to the deflections of unipolar

direct leads from the anterior surface of the right ventricle. One method of analyzing the QRS deflections of direct leads of this kind is to regard them as depicting the electrical forces produced by the part of the ventricular wall in contact with the exploring electrode, measured from a fluctuating base line which represents the potential variations of the adjacent ventricular cavity. In a similar way we may regard the potential variations of the cavity of the right ventricle which occur during a period when its septal wall, but not its free wall, is undergoing activation, as changes in potential produced by the septal muscle plotted upon the time-course of the potential of the left ventricular cavity as reference level. In right bundle branch block the cavity of the left ventricle is negative throughout the QRS interval while that of the right ventricle is initially positive. It is clear that this initial positivity is due to activation of the septum from left to right. Since it occurs before activation of the free wall of the right ventricle has begun, it is transmitted to the epicardial surface of this wall and to the right side of the precordium. An initial R wave in the leads from the right side of the precordium in complete and incomplete right bundle branch block is therefore ascribed to forces produced by the spread of the impulse through the septum from left to right.

When the initial component of QRS has almost exactly the same form when intraventricular conduction appears to be normal as when complete right bundle branch block is present, as in the case illustrated by Figs. 1 and 2, it is difficult to avoid the conclusion that it represents the same phenomenon in both cases. It was shown long ago[4] that in dogs, leads from the cavity of the right ventricle often display a small initial R deflection indicating that the left side of the septum is activated before the right side. Recently, leads from the cavity of the human right ventricle have demonstrated that this is regularly the case in man.[5] It is highly probable, therefore, that the resemblance in question is not peculiar to cases of partial right bundle branch block, and that in most, if not all, normal electrocardiograms the initial R wave in Lead V_1 is mainly of septal origin. It can, however, hardly be due to septal forces alone, for this lead displays a small initial R wave in the majority of the cases of left bundle branch block in which this deflection must represent forces produced by activation of the free wall of the right ventricle. When intraventricular conduction is normal, or nearly so, there is no way of estimating in a given instance how much of the initial R wave of Lead V_1, or some other lead from the right side of the precordium, is contributed by forces arising in this wall and how much by forces generated in the septum. The early and rapid development of strong forces, opposed to both of these, in the free wall of the left ventricle makes it hard to ascertain the time-course of those produced by that of the right. These opposing left ventricular forces make the initial R wave of the leads from the right side of the precordium much smaller than it would otherwise be both in right bundle branch block, complete or incomplete, and when no conduction defect is present. It is probable that they are mainly responsible for the distinct separation of the R and R′ deflections of the former. It is noteworthy that no similar separation occurs in the leads from the left side of the precordium in left bundle branch block and that in right bundle branch block the early large R wave of these leads is

simultaneous or nearly simultaneous with the cleft between the R and R′ waves in the leads from the right side.

In right bundle branch block two of the four sets of forces generated by excitation of the ventricular myocardium are altered with respect to the time of their occurrence, to their polarity, or to both. The forces produced by all or part of the right half of the septum are generated abnormally late in the QRS interval and their polarity is reversed, so that they tend to make both the cavity of the right ventricle and the epicardial surface of this chamber positive instead of negative. The forces produced by the free wall of the right ventricle are delayed still more, but their polarity is not affected. In incomplete right bundle branch block there is no reason to suppose that their magnitude is abnormal or that the order in which the various parts of the free wall of the right ventricle become active is modified. In complete right bundle branch block, however, the contrary is probably the case, for the excitatory impulse reaches the right ventricle by an abnormal route and presumably spreads over the right ventricular muscle in an abnormal fashion. It seems likely that the general course of the impulse from right to left over this muscle gives rise to some electrical forces which are tangential to the inner and outer boundaries of the parts of the wall in which they are generated.[6] Such forces would tend to make the right side of the precordium more positive than it would be if the order of activation of the different fractions of the free wall of the right ventricle were normal.

It is clear that when the R′ deflection is the terminal component of the QRS complex of the leads from the right side of the precordium, the latest part of it must be ascribed to forces produced by late activation of some part of the free wall of the right ventricle. The origin of the earlier fractions of this deflection can only be ascertained with certainity by comparing them with the simultaneous deflections of leads from the cavity of the right ventricle. In canine right bundle branch block, such leads usually display a tiny preliminary upward deflection followed by a moderately tall R wave which is succeeded by an S wave of approximately equal voltage. In epicardial and precordial leads the preliminary deflection is clearly visible, but the main septal R wave is fused with the upward deflection produced by activation of the free wall of the right ventricle to form a broad R′ wave, which usually displays on its ascending limb a notch marking the junction of its two components.[7] We must assume, then, that in human right bundle branch block the earliest part of the R′ deflection of the leads from the right side of the precordium is sometimes, if not always, due in part to forces of septal origin.

Consider now the differences between complete and incomplete right bundle branch block and between the different grades of incomplete right bundle branch block with regard to the times of occurrence and magnitudes of the two sets of forces tending to make the right side of the precordium positive during the latter part of the QRS interval. Any abnormal septal forces, due to activation of some part of the right half of the septum from left to right instead of in the opposite direction, which may be present must begin at the same time with respect to the onset of the first QRS deflection, regardless of the grade of the conduction

defect. On the other hand, the magnitude and duration, perhaps only the duration, of these forces must be proportional to the delay in the activation of the right ventricle. The magnitude of the forces produced by the free wall of this chamber may be considerably smaller in incomplete than in complete right bundle branch block, but in all grades of the former it must be the same. The time of occurrence of these forces in the QRS interval, unlike that of the septal forces, measures exactly the grade of the conduction defect. The area of the QRS deflections in any given lead is determined by the direction in which the various parts of the ventricular myocardium are activated and not by the times of their activation.[8] In right bundle branch block, the change in the area of QRS due to the reversal of the direction in which a part or all of the right half of the septum is activated should be twice as large as the change in area that would be produced by the replacement of this part of the septum by scar tissue. On the other hand, if we disregard the tangential forces mentioned in a previous paragraph, the area contributed to QRS by activation of the free wall of the right ventricle should be the same in all grades of right bundle branch block.

It is not difficult to understand why the R′ deflection of the leads from the right side of the precordium is so much smaller in incomplete than in complete right bundle branch block. If the first part of this deflection is of septal origin, we can also understand why its upstroke may begin at the same time in the QRS interval in both cases. In Leads V_1 and V_{r3} of Fig. 3, the R′ deflection of the second of the paired complexes begins at the same time and at the same level as that of the first. In Leads V_2, V_3, V_4, and V_E it begins at a slightly higher level and perhaps a trifle earlier in the QRS interval. In all of the leads from the right side of the precordium, the reduction in the grade of the block caused a shift of the apex of the R′ wave toward the beginning of the QRS interval greater than the decrease in the length of this interval which it produced (Fig. 4). In Fig. 6 the decrease in the size of the R′ deflection in Leads V_1 and V_E as the grade of the block diminished is very striking; in the latter lead this deflection disappeared altogether. The initial R deflection did not change. In Leads V_2 and V_3 the second R wave of the first record shifted toward the beginning of the QRS interval as the grade of the block diminished, for in the later records this deflection is clearly superimposed upon the initial R wave, which has become much taller. Its behavior suggests that it represents forces generated by the free wall of the right ventricle rather than by the septum. It is obvious that the relative magnitude of the septal and free-wall components of the R′ deflection may vary greatly from lead to lead. This is in no way surprising.

INCOMPLETE RIGHT BUNDLE BRANCH BLOCK VERSUS LOCAL BLOCK

The question arises as to whether it is possible to distinguish with certainty, by means of precordial leads, between incomplete right bundle branch block, as we have defined it, and a defect in conduction located in one of the subdivisions of the right branch of the bundle of His or in the right Purkinje plexus. In the former the intrinsic deflection would be equally delayed in unipolar leads from every part of the right ventricular surface; in the latter this

deflection would be abnormally late only in the leads from that part of the ventricular wall supplied by the subdivision or the part of the plexus, affected. In incomplete right bundle branch block evidence of a delay in the activation of the surface of the right ventricle would, therefore, be expected to appear in all unipolar precordial leads in which the exploring electrode is placed much closer to this surface than to that of the left ventricle. In block affecting a subdivision of the right bundle branch, on the other hand, one would expect to find such evidence in some of these leads, but not in others. It is for this reason that we have classified our cases with respect to the number of leads from the right side of the precordium showing a secondary R wave. We felt, for example, that the evidence pointing to the presence of incomplete right bundle branch block was much stronger when there was a conspicuous R′ deflection in both Lead V_1 and Lead V_E, which are from points relatively far apart and presumably reflect the potential variations of quite different parts of the right ventricular surface, than when such a deflection was present in Lead V_1 only. Consequently, the class to which a given electrocardiogram was assigned indicates, in some measure, our opinion as to the probability that it represents incomplete right bundle branch block. When the R′ deflection is present in only one precordial lead, the possibility that it is the result of local block, or has some other origin, must be seriously considered. We do not, however, by any means believe that incomplete right bundle branch block can be excluded under these circumstances. It will be noted that in both Fig. 3 and Fig. 6, the number of leads which display an R′ deflection is larger when the prolongation of the QRS interval is greater. It seems much more likely that each of these figures represents variations in the grade of a single conduction defect, than that each of them represents two or more distinct conduction defects. The latter possibility cannot, perhaps, be excluded with finality.

It should be pointed out in this connection that although unipolar precordial leads resemble unipolar direct leads in many ways, they differ from them in one important respect. The latter record the potential variations of a single point on the epicardial surface, whereas the former depict a mixture of the potential variations of all parts of the ventricular surfaces in which the potential changes of the nearest parts of this surface are ordinarily the dominant components. It is not necessarily true that the precordial area which yields evidence of delayed activation of the right ventricle when there is a minor delay in the transmission of the impulse through the right branch of the bundle of His will coincide exactly with the precordial area that yields similar evidence when complete right bundle branch block is present. In both cases the size and the location of the area in question are affected by many factors, such as the distance of the anterior wall of the heart from the surface of the precordium, the position of the heart as a whole, and rotation of the heart about its long axis.

THE QRS INTERVAL

In hearts of normal size the free wall of the left ventricle is approximately three times as thick as that of the free wall of the right. If the excitatory impulse spreads through both walls with the same speed, activation of the left

ventricular wall should take much longer than that of the right. The duration of QRS is normally determined, then, by the length of time it takes the excitation process to pass from the endocardial to the epicardial surface of the thickest part of the free wall of the left ventricle. Theoretically, therefore, it is possible in incomplete right bundle branch block of minor degree to have a QRS interval of normal length. In slightly less than one-half of our cases, the QRS interval was less than 0.10 second (Table II), while in the others it was between 0.10 and 0.12 second.

TABLE II. THE QRS INTERVAL

GROUP NO.	LONGEST (SECOND)	SHORTEST (SECOND)	AVERAGE (SECOND)	NUMBER OF CASES		
				0.10 SECOND OR MORE	LESS THAN 0.10 SECOND	TOTAL
I	0.115	0.08	0.099	17	10	27
II	0.115	0.08	0.097	11	9	20
III	0.11	0.08	0.91	8	3	11
IV, A	0.115	0.08	0.105	7	3	10
IV, B	0.11	0.07*	0.087	2	5	7
IV, C	0.10	0.09	0.091	2	4	6
IV, D	0.11	0.09	0.10	3	2	5
V	0.11	0.09	0.099	5	3	8
VI	0.10	0.09	0.095	1	1	2
VII	0.08	0.08	0.08	0	1	1
				55	41	97

*In a child six years old.

At times it is difficult to know with certainty whether an electrocardiogram which displays a QRS interval measuring between 0.10 and 0.12 second represents incomplete or complete right bundle branch block, particularly when the deflections of the leads from the right side of the precordium have a configuration which closely resembles that produced by the latter. Since the QRS duration of some normal electrocardiograms does not exceed 0.06 or 0.07 second, it is quite possible that complete right bundle branch block may sometimes be present when the QRS interval is less than 0.12 second. Clearly, no hard and fast line can be drawn between high grade incomplete right bundle branch block, on the one hand, and complete right bundle branch block, on the other.

CONFIGURATION OF THE COMPLEXES OF THE PRECORDIAL LEADS

The various electrocardiographic patterns considered diagnostic or strongly suggestive of incomplete right bundle branch block are illustrated in Fig. 7. The curves of this figure are arranged from above downward in the order of the groups in which they fall on the basis of the criteria given in an earlier section of this article.

The uppermost row of tracings (*A*) are the precordial leads of a woman with extensive scleroderma. A previous electrocardiogram, taken on May 24,

1944, was considered to be within normal limits. The tracing reproduced, which was taken on March 29, 1946, shows broad S waves in Lead I, which were not present in the earlier record. The QRS interval is the same in both tracings and measures 0.09 second in the limb leads. There are primary and secondary R

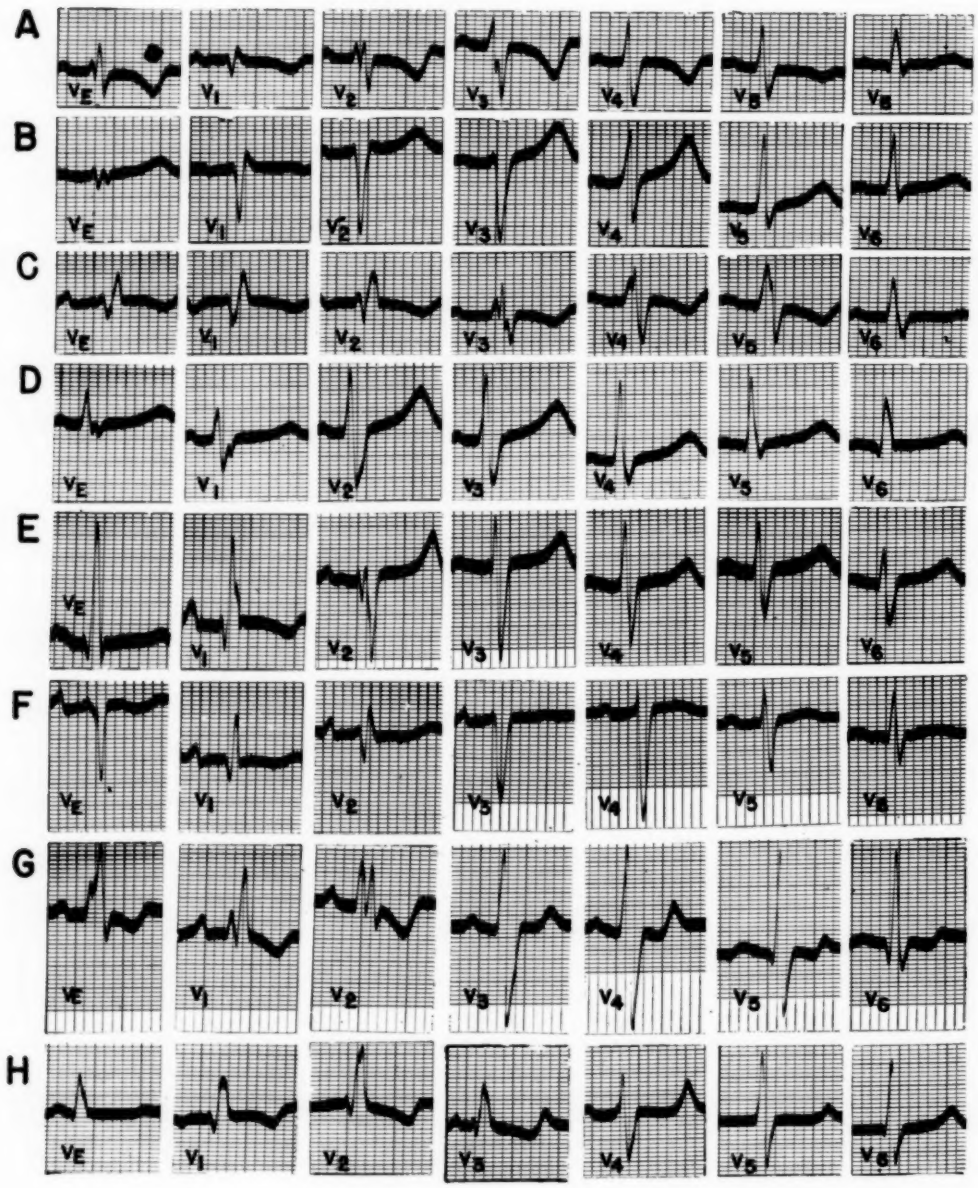

Fig. 7.—Various types of incomplete right bundle branch block (*A*, *B*, *C*, *D*) and of incomplete right bundle branch block associated with right ventricular enlargement (*E*, *F*, *G*, *H*).

deflections, approximately equal in size, and an S wave, a little over 2 mm. in depth, in Lead V_1. In Lead V_2, the QRS complex consists of two small R waves followed by a prominent S wave. This lead is from the edge of the transitional zone. The complexes of the leads from the left side of the precordium (V_5 and V_6) are essentially normal in general outline. The deflections of Lead V_E are somewhat like those of Lead V_2. This tracing belongs, therefore, to Group I, Class a.

The precordial electrocardiogram in the second row (*B*) of Fig. 7 is that of a man 38 years of age whose extremity leads suggested the possibility of incomplete right bundle branch block. This was the reason for taking chest leads. There were no clinical findings referable to the heart; the cardiac examination was part of a routine physical checkup. In the tracing of Oct. 29, 1942, Lead V_1 shows small R and R′ waves separated by a deep S deflection. In the leads from the left side of the precordium there are tall R waves followed by rather broad S waves. Leads V_3 and V_4 show QRS complexes which are transitional in form. The transitional zone is, therefore, in the usual position. This tracing was placed in Group II. Since there are signs of the conduction defect in the first two precordial leads and in Lead V_E, it belongs to Class a.

The third set of curves (*C* of Fig. 7), taken on May 27, 1943, are those of a 72-year-old man with coronary atherosclerosis. There is a prominent S wave in Lead I, and the QRS interval in the limb leads measures 0.11 second. The leads from the right side of the precordium, including Lead V_E, show a small initial R deflection followed by a rather deep S wave and a final R′ deflection which is comparatively tall. The leads from the left side of the precordium show rather tall R waves followed by broad S waves. This is an example of the curves placed in Group II, B. An electrocardiogram (not reproduced here) taken on Aug. 4, 1943, on this man is strongly suggestive of complete left bundle branch block, although the usual series of precordial leads did not cross the transitional zone. There were evidently bilateral bundle branch lesions in this patient, leading first to incomplete right bundle branch block and later to complete interruption of conduction on the left side.

The fourth tracing (*D* of Fig. 7) is a sample of the precordial records placed in Group III, Class c. The patient was a 48-year-old man with functional hypoglycemia. There were no demonstrable abnormalities on physical examination. The blood pressure was 120/70. Leads V_1 and V_E of the tracing taken on Oct. 29, 1942, show a relatively tall primary R deflection followed by an S wave, in the trough of which there is a small embryonic R′ deflection. As far as the R′ deflection is concerned, these complexes resemble those often seen in leads from points farther to the left: compare Leads V_3 and V_4 of Fig. 1 with Lead V_1 of the present case. They are transitional in form between the complexes we have described as occurring in the leads from the right side of the precordium in the curves of Groups I and II and those which are found in the leads from the left side of the precordium. Eleven patients of this group show embryonic R′ waves in the leads from the right side of the precordium. This characteristic indicates that the transitional zone is shifted far to the right, probably because of rotation of the heart in a clockwise direction about an axis pointing from

the apex toward the base. In three of the patients belonging to Group III, additional leads were taken from the right side of the chest (V_{r3} and V_{r4}). These show typical M-shaped QRS complexes of the type usually seen in Lead V_1 in cases of Group I and Group II (Fig. 8).

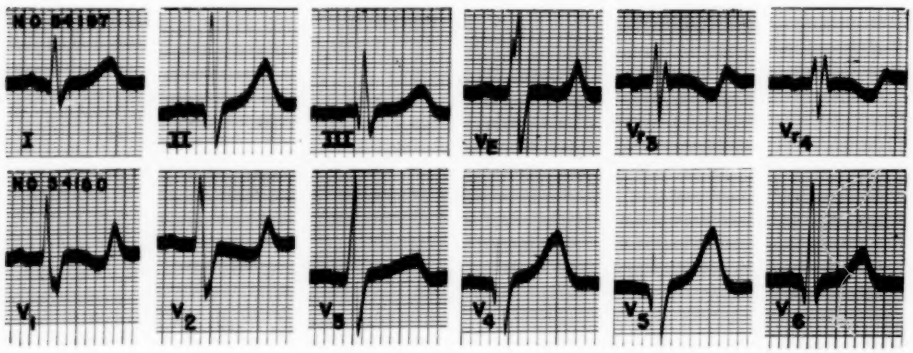

Fig. 8.—Incomplete right bundle branch block with displacement of the transitional zone to the right. Congenital anomaly of the heart (interventricular septal defect) in a girl 3½ years old.

The last four precordial electrocardiograms (*E*, *F*, *G*, and *H* of Fig. 7) are examples of the types found in incomplete right bundle branch block complicated by right ventricular hypertrophy, and are described in a later section.

THE TRANSITIONAL ZONE AND THE VALUE OF ADDITIONAL LEADS FROM THE RIGHT SIDE OF THE CHEST

As we have indicated in the section on classification, the class in which a given electrocardiogram was placed is an index of our opinion as to the probability that it represents incomplete right bundle branch block. It has been pointed out that in incomplete right bundle branch block one would expect to find evidence of late activation of the right ventricle in all of the leads from the right side of the precordium. A localized conduction defect involving the Purkinje network in a limited area, on the other hand, would be expected to affect only those leads in which the exploring electrode was placed directly over the region where activation was delayed. When the expected changes occur in Lead V_1 only (Class d) or are confined to Leads V_1 and V_2 (Class b), the diagnosis of incomplete right bundle branch block is made with some hesitation. If, however, there is a late R′ deflection in both Lead V_1 and Lead V_E, which are from points far apart and must reflect the potential variations of quite different parts of the right ventricular surface, the diagnosis is made with greater confidence.

The main difference between the cases placed in Group III and those of the two preceding groups is that the transitional zone is farther to the right in those placed in Group III, so that the characteristic R and R′ waves are not found in the leads from the right side of the precordium. This observation led us to take additional leads from the right side of the chest (V_{r3}, V_{r4}, etc.), and in every case in which they were used, they displayed double R waves of the kind usually

found in Leads V_1, V_2, and V_E. Data with respect to the kinds of cases in which such leads were taken are given in Table II. The value of these leads in substantiating the diagnosis of incomplete right bundle branch block is considerable, and it is recommended that they be employed whenever the limb leads and the leads from the right side of the precordium are suggestive, but not diagnostic, of this conduction defect. It must be remembered, however, that the farther the exploring electrode from the surface of the heart, the less accurately does the lead portray the potential variations of the nearest parts of the ventricular surface, and the more difficult is the interpretation of the ventricular deflections. It is conceivable that the leads under consideration may, under some circumstances, lead to an erroneous diagnosis of incomplete right bundle branch block.

There were five cases in Class d and two in Class b in which additional leads from the right side of the chest were taken (Table III). All these showed evidence of late activation of the right ventricle. We have, therefore, considered these cases examples of incomplete right bundle branch block. In the tables there are columns headed "Certain" and others headed "Probable." Under the former heading we have placed the cases of all classes except Class d, plus cases of alternating complete and incomplete right bundle branch block. There may be some question as to the correct diagnosis in the cases of Class b in which no additional leads from the right side of the chest were taken. Because these cases resembled closely those in which such leads supported the diagnosis of incomplete right bundle branch block, and for the purpose of simplifying our classification and discussion, we have placed these cases with those which display more reliable evidence of the presence of this conduction defect.

TABLE III. CASES IN WHICH THE CLINICAL DIAGNOSIS WAS CONFIRMED OR ESTABLISHED BY ADDITIONAL LEADS TO THE RIGHT, CORRELATED WITH THE GROUPS AND SUBGROUPS INTO WHICH THEY WERE CLASSIFIED

GROUP	a	b	c	d	TOTAL
I	3	1	0	1	5
II	1	0	0	1	2
III	0	1	0	4	5
IV, A	2	0	0	0	2
V	1	0	0	0	1
VI	2	0	0	0	2
VII	—	—	—	—	1
Total	9	2	0	6	17

The electrocardiogram reproduced in Fig. 8 is that of a girl 3½ years old. She was studied in the Pediatrics Outpatient Department of the University Hospital in August, 1945, because of anorexia, sleeplessness, and listlessness following an episode of otitis media one month earlier. She was not cyanotic at birth, but a few days later a diagnosis of congenital heart disease was made. Growth and development were about normal. Examination of the heart revealed a diffuse apical impulse. A faint systolic murmur was heard over the

entire precordium, but was loudest in the third and fourth intercostal spaces to the left of the sternum. These findings were considered suggestive of an intraventricular septal defect. The electrocardiogram of Sept. 10, 1945, shows prominent R waves and conspicuous S waves in the three standard limb leads. The QRS interval measures 0.08 second. Lead V_1 displays a rather tall R wave followed by an S wave, in the trough of which there is an embryonic R′ wave. Leads V_1, V_2, and V_3 exhibit QRS complexes similar to the kind usually found in Leads V_3 and V_4. They are transitional between those normally found in the leads from the right side of the precordium and the type normally found in the leads from the left side. The transitional zone is, therefore, far to the right. It was not crossed by the standard precordial leads. The leads from the left side of the precordium show a tall R wave preceded by a Q wave and followed by an S deflection. The potential variations of the tip of the ensiform process (V_E) are also of transitional form, and the R peak displays a prominent notch. In order to obtain curves from points to the right of the transitional zone, Leads V_{r3} and V_{r4} were taken. These show double R waves of the kind we have described as indicative of incomplete right bundle branch block. Note the similarity, apart from the duration of the QRS interval, between the complexes of Lead V_1 in the present case and those of Lead V_4 in Fig. 6 (top row), which is one of a series of precordial leads that is characteristic of right bundle branch block, with the transitional zone a little to the left of the usual position. The potential variations of the left leg (V_F) resemble those of the left precordium (V_5 and V_6), while the potential variations of the left arm (V_L) are small. The heart was, therefore, in the semivertical position.

An even more striking example of the influence of the position of the transitional zone upon the configuration of the precordial electrocardiogram in incomplete right bundle branch block is shown in Fig. 9. The patient was a 17-year-old boy who was studied in the Outpatient Department of the University Hospital on April 13 and 14, 1944. He was not blue at birth. When he was one year old his parents noticed that the pulsations of his heart were unusually conspicuous, but the physician who was consulted reassured them. In 1935 the boy was told that he had heart trouble and that he should limit his activity to some extent. Two years previous to the examination at this hospital he had rheumatic fever and was in bed for two months. During this time he had conspicuous cyanosis of the lips and nail beds. Examination of the heart revealed an intense thrill in the pulmonic area and along the left border of the sternum. In the same region there was a Grade V rasping systolic murmur which was transmitted to the left. The heart was not enlarged. There was no cyanosis or acral clubbing. Although there was some uncertainty as to the proper diagnosis, the lesion was thought to be an auricular septal defect or pulmonic stenosis.

The electrocardiogram of April 14, 1944, shows broad S waves in all three standard limb leads. There is a relatively large Q deflection in Lead I. The QRS interval measures 0.09 second. There is a prominent late R wave in Lead V_R. Leads V_1 to V_6 all display QRS complexes of transitional form. Leads V_1 and V_E show a slur on the upstroke of the R wave. Lead V_7 exhibits small complexes with broad S waves; in Lead V_8 the deflections are still smaller, but

of the same general outline. In Lead D_{viii} there are very small primary and secondary R deflections separated by a deep S deflection. The transitional zone in the back lies between Lead V_8 and Lead D_{viii}. Primary and secondary R deflections are present in Leads V_{r8}, V_{r7}, V_{r6}, and V_{r5}, and the configuration of the QRS complex in these leads suggests delayed activation of the right ventricle. There is fusion of the two R waves in Lead V_{r5}. Lead V_{r4} is near the border

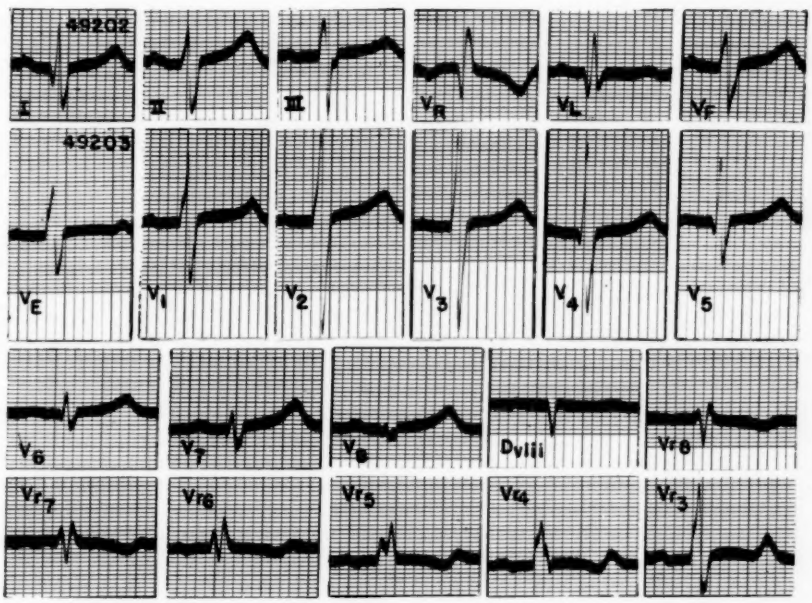

Fig. 9.—Incomplete right bundle branch block in a case of congenital cardiac anomaly (atrial septal defect or pulmonic stenosis). Transitional zone displaced to the right. V_{r3}, V_{r4}, etc., are leads from the right side of the chest corresponding to V_3, V_4, etc., from the left side. V_7 is a lead from the left posterior axillary line, V_8 a lead from the left back. D_{viii} is a lead from the eighth dorsal spine.

of the transitional zone in front, and transitional complexes are present in Lead V_{r3}. These tracings display a very broad transitional zone, with extreme displacement of its boundaries to the left and to the right. They illustrate the value of additional leads from points to the right of the right sternal margin when the usual precordial leads fail to cross the transitional zone.

INCOMPLETE RIGHT BUNDLE BRANCH BLOCK AND RIGHT VENTRICULAR HYPERTROPHY

When incomplete right bundle branch block is associated with right ventricular hypertrophy there is characteristically a tall secondary R deflection in the leads from the right side of the precordium. The leads from the left side often show a small R deflection followed by a small S deflection. The pattern is, in general, similar to that seen in right ventricular hypertrophy uncomplicated by incomplete right bundle branch block. Those electrocardiograms

TABLE IV. CORRELATION WITH CLINICAL DIAGNOSIS

	GROUP I		GROUP II		GROUP III		GROUP IV						TOTAL
							A		B		C	D	
	CERTAIN	PROBABLE	CERTAIN	PROBABLE	CERTAIN	PROBABLE	CERTAIN	PROBABLE	CERTAIN	PROBABLE	CERTAIN	CERTAIN	
Number													
Males	16	0	19	2	9	7	7	1	6	1	3	2	
Females	11	1	1	0	2	1	3	0	1	0	3	3	
Totals	27	1	20	2	11	8	10	1	7	1	6	5	
Average age													
Males	41.5	—	41.1	38.5	47.9	35.0	40.4	22.0	28.6	34.0	17.3	33.0	
Females	34.0	64.0	41.0	—	31.0	11.0	16.3	—	50.0	—	44.7	37.5	
Mitral stenosis	4	—	—	—	—	—	3	—	3	1	2	4	17
Mitral stenosis plus aortic valvular lesion	5	—	2	—	—	—	—	—	1	—	1	—	9
Congenital heart disease	—	—	1	—	—	—	—	—	—	—	—	—	1
I. V. septal defect*	1	—	1	—	1	1	2	—	—	—	—	—	5
Tetralogy of Fallot	—	—	—	—	—	—	1	—	1	—	—	—	2
Lutembacher's syndrome	1	—	—	—	—	—	—	—	—	—	—	—	1
Patent ductus arteriosus	—	—	—	—	—	1	—	—	—	—	—	—	1
I. A. septal defect†	—	—	—	—	1	—	—	—	—	—	1	—	2
Cor pulmonale (chronic)	—	—	2	—	1	—	4	1	1	—	—	—	9
Essential hypertension	1	—	1	—	—	1	—	—	—	—	—	—	3
Hypertensive heart disease	—	—	1	—	2	—	—	—	—	—	—	—	3
Arteriosclerotic heart disease (coronary)*	5	—	—	—	1	—	—	—	1	—	1	—	8
Other left-sided lesions	—	—	1	—	—	—	—	—	—	—	—	—	1
Heart disease (etiology?)	1	—	—	—	—	—	—	—	—	—	—	—	1
Possible heart disease	2	—	2	—	2	2	—	—	—	—	1	—	8
Potential heart disease	2	—	1	—	1	—	—	—	—	—	—	—	4
No heart disease	5	—	8	2	2	3	—	—	—	—	—	—	20
Totals	27	1	20	2	11	8	10	1	7	1	6	5	

*Without myocardial infarction.
†One case in each group had a paroxysmal arrhythmia.

which displayed a tall R′ wave in Leads V_1 and V_2 were placed in Group IV (*A*, *B*, *C*, and *D*). The various QRS configurations encountered are illustrated in Fig. 7 (*E*, *F*, *G*, and *H*). In addition to changes suggestive of incomplete right bundle branch block, all of these patients showed definite right axis deviation in the limb leads. With one exception the clinical diagnoses made were consistent with the presence of right ventricular hypertrophy (Table IV).

A precordial electrocardiogram which is representative of Group IV, A is reproduced in Fig. 7,*E*. It was taken on Nov. 20, 1945. The patient was a man 22 years of age with physical signs typical of the tetralogy of Fallot. The standard limb leads show right axis deviation and large P waves in Lead II. The unipolar extremity leads indicate that the heart was in the vertical or semivertical position. Leads V_1 and V_E display a small initial R wave and a very tall R′ deflection. The leads from the left side of the precordium, and

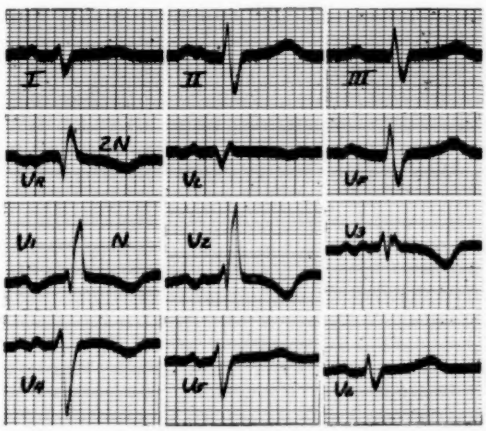

Fig. 10.—Incomplete right bundle branch block associated with right ventricular enlargement. The patient was a 42-year-old man with rheumatic mitral stenosis and aortic regurgitation. Note large secondary R waves in Leads V_1 and V_2.

especially Lead V_6, show smaller QRS deflections, with R and S waves of nearly equal size. In this particular instance the transitional zone begins with Lead V_2; it is not uncommon to find this zone displaced somewhat to the right in cases of the kind under consideration. The pattern is the reverse of that seen in incomplete right bundle branch block without right ventricular hypertrophy, with regard to the size of the R′ wave in the leads from the right side of the precordium in comparison with that of the R wave in the leads from the left side.

Another example of the tracings placed in Group IV is reproduced in Fig. 10. This electrocardiogram is that of a man, 42 years of age with rheumatic heart disease, mitral stenosis, and aortic regurgitation. Roentgenographic examination, including orthodiagraphy, showed cardiac enlargement, left auricular

enlargement, and calcification of the mitral valve. Large deformed P waves suggestive of auricular enlargement and consistent with the diagnosis of mitral stenosis are present in Leads I and II. The P-R interval measures 0.21 second and the QRS interval, 0.08 second. There are large S waves in Leads I, II, and III, and a broad, late R wave in Lead V_R. Since the potential variations of the left leg resemble those of the left side of the precordium, and the deflections of Lead V_L are small, the heart was in the semivertical position. Leads V_1 and V_2 show a small initial R wave followed a very tall R′ deflection. The latter is a little larger in Lead V_2 than in Lead V_1. The leads from the left side of the precordium (V_5 and V_6) display rather small QRS deflections with rather broad S waves. The other precordial leads (V_3 and V_4) exhibit complexes transitional in form between those found in the leads from the right, and those found in the leads from the left side of the precordium. The large secondary R wave in the leads from the right side diminishes rather rapidly in the leads from points farther to the left, and there is no sign of it in Lead V_4. This is a fairly typical example of the pattern seen in the precordial leads when incomplete right bundle branch block is associated with right ventricular hypertrophy.

The electrocardiogram reproduced in Fig. 7,*F* was taken on Feb. 16, 1943. The patient was a man 35 years of age who had suffered since infancy from a chronic cough productive of foul sputum. There was a history of several attacks of "pneumonia" during the six years previous to the examination, and of increasingly severe dyspnea, upper abdominal pain, and slight edema of the ankles during the two weeks preceding the examination. His general health had been poor. Roentgenographic examination of the chest revealed widespread, patchy pneumonitis, perihilar infiltration, and thickening of the pleura at both apices. These findings were considered highly suggestive of bronchiectasis. The heart was moderately enlarged. The blood pressure was 110/74. Clubbing of the fingers and toes and obvious acral cyanosis were present. The patient did not return for further studies.

The electrocardiogram shows slight right axis deviation, and unusually large P waves and inverted T waves in Leads II and III. The QRS interval measured 0.08 second in the limb leads. Leads V_1 and V_2 show double R waves, indicating a delay in activation of the right ventricle. The R′ deflection is relatively tall in Lead V_1 and measures about 9.5 millimeters. Lead V_E shows a small initial R wave followed by a deep S deflection. The complexes of Lead V_2 are transitional in form between those of Lead V_1 and those of Lead V_3. The QRS complexes of the midprecordial leads (V_3 and V_4) are of unusual outline in that they consist of a small R wave followed by a deep S deflection, while those of Lead V_5 appear to be transitional in form between the complexes of Lead V_4 and those of Lead V_6. The R wave of the latter is only slightly smaller than the R′ deflection of Lead V_1 and is followed by a prominent S wave.

Some of the features seen in this tracing are rather difficult to explain satisfactorily. The leads from the right side of the precordium are rather strongly suggestive of incomplete right bundle branch block, and the tall R′ deflection in Lead V_1, together with the clinical impression of cor pulmonale, makes it highly probable that a right ventricular hypertrophy was present. The factors re-

sponsible for the QRS pattern seen in the midprecordial leads are not obvious, but this configuration indicates that the main electrical forces acting on the midprecordium had an anteroposterior direction. It seems probable that this pattern is the result of some peculiarity in the position of the heart which led to an unusual distribution of the areas on the surface of the chest to which the potential variations of the two ventricular surfaces were transmitted. It may be mentioned in this connection that the leads from the extreme right side of the precordium are from points relatively near the thick basal parts of the right ventricular wall, whereas those from the midprecordium are from points closer to the thinner central and apical parts of this wall. In animals, leads from the base of the right ventricle show large R waves, while those from the central region and apex show small R waves. It is possible that under some circumstances the precordial leads may be affected in the same way.

The tracing reproduced in Fig. 7,*G* is an example of those placed in Group IV, Class c. The patient was a 9-year-old boy who at the age of 7 had begun to tire easily, to become dyspneic, and to develop anorexia. There was no known episode of acute rheumatic infection. When he was 8 years old, a cardiac murmur was discovered. A few months later edema of the ankles developed, and during the following two weeks he was orthopneic. Two months prior to hospital admission, ascites, sufficient in amount to require two paracenteses, appeared, and was accompanied by nocturnal dyspnea. On examination, the heart was found to be greatly enlarged both to the right and to the left. A loud systolic and a rumbling diastolic murmur were heard at the apex, and there was a rather faint, short diastolic murmur along the left edge of the sternum. The blood pressure was 120/40. An orthodiagram and film studies of the chest showed generalized cardiac enlargement with a moderate degree of pulmonary congestion. There was pronounced diminution of the retrocardiac space as well as deformity of the anterior thoracic wall as a result of tremendous cardiac dilatation. The diagnosis was rheumatic heart disease, mitral stenosis, and aortic regurgitation, but the possibility of the presence of an interatrial septal defect could not be excluded.

The electrocardiogram taken on June 7, 1945, shows right axis deviation and a QRS interval of 0.10 second in the limb leads. The P waves are unusually large and broad and suggest auricular enlargement. The leads from the right side of the precordium (V_1 and V_2) and from the tip of the ensiform process (V_E) display complexes of the kind we have described as characteristic of incomplete right bundle branch block plus right ventricular hypertrophy. The transition from complexes of the kind seen in the first to complexes of the kind seen in the last leads of the precordial series begins with Lead V_2 and ends with Lead V_5. Lead V_6 shows a very tall R wave, which, again, is an unusual feature not easily explained.

The last set (*H*) of precordial leads in Fig. 7 is a representative of Group IV, d. The patient was a 35-year-old man who was studied at the University Hospital in December, 1943. During the preceding three years he had had several episodes of hemoptysis following strenuous exertion. He had been a "blue baby" and for many years his friends had commented on his blue color,

and particularly on his blue-black lips. From childhood he had become purple on moderate exertion. He had been told on several occasions that there was something wrong with his heart, and had had clubbing of the fingers and toes as long as he could remember. Examination revealed moderate acral cyanosis. The precordial area was prominent. The heart was moderately enlarged to the left. At the apex there was a loud, low-pitched, coarse diastolic murmur ending in a snapping first sound. There were variations in the intensity of this sound. Along the left border of the sternum there was a faint, high-pitched diastolic murmur. The blood pressure was 104/70. The hemoglobin was 142 per cent. Roentgenographic examination showed pronounced enlargement of the pulmonary conus and the pulmonary vessels. The increase in the size of these vessels was so great as to lead to a suspicion of aneurysm of the pulmonary artery. There was also transposition of the thoracic aorta. The heart was moderately enlarged in all diameters, but there was no evidence of atrial enlargement. The proper anatomic diagnosis was thought to be interatrial septal defect.

The electrocardiogram of Dec. 20, 1943, revealed that from time to time idioventricular rhythm was present, and that the rate of this rhythm was fast enough to cause A-V dissociation. This accounts for the variations in the position of the P wave in the illustration. Leads V_E, V_1, and V_2 were taken with the electrocardiograph operating at its normal sensitivity; the other precordial leads were taken with the instrument at one-half the normal sensitivity. The QRS interval measures 0.08 second in the limb leads. The leads from the right side of the precordium (V_1 and V_2) show small initial R deflections and tall R′ waves similar to those we have described as characteristic of this group. The same QRS configuration is present in Lead V_3, and a remnant of the primary R can be seen at the base of the main upward deflection in Lead V_4. Besides a slight shift of the transitional zone to the left, the sequence of changes suggests that the secondary R wave moved toward the beginning of the QRS group and engulfed the primary R wave as the exploring electrode was moved from right to left. The leads from the left side of the precordium display a prominent early R deflection followed by a conspicuous S wave. The transitional zone is not well defined, but the late R wave of Leads V_1, V_2, and V_3 is replaced by an S deflection in Leads V_4, V_5, and V_6.

The factors responsible for the large R′ deflection in the leads from the right side of the precordium in incomplete right bundle branch block associated with right ventricular hypertrophy are no doubt the same as those that give rise to the abnormally large QRS deflections both in uncomplicated hypertrophy of the left and in uncomplicated hypertrophy of the right ventricle. In attempts to explain these abnormally large deflections it has been suggested that: (1) Because the solid angle subtended at the exploring electrode by the extensive surface area of the hypertrophied ventricle is abnormally large, the effect of the enlarged ventricle upon the potential variations of this electrode is much the same as if it were moved closer to the epicardial surface. (2) In ventricular hypertrophy the cross-sectional area of each individual muscle fiber is increased. Increasing the cross-sectional area of a muscle fiber reduces its internal resistance, but leaves unchanged the external resistance in the circuits involved in excitation.

Since the voltage drop in each part of the circuit is proportional to the ratio of the resistance of that part to the total resistance in the circuit, the effect of increasing the size of the fiber is to increase the magnitude of the potential variations over its external surface produced by the spread of the excitatory process.

Probably the increased voltage of the electrocardiographic deflections in ventricular hypertrophy is due to a combination of several factors. When incomplete right bundle branch block is associated with right ventricular hypertrophy, the increased voltage developed during activation of the free wall of the right ventricle, and perhaps during activation of the right half of the septum also, gives rise to the very tall secondary R wave recorded in the leads from the right side of the precordium.

INCOMPLETE RIGHT BUNDLE BRANCH BLOCK AND LEFT VENTRICULAR HYPERTROPHY

In four of the cases of right bundle branch block which we studied, it was thought that the defect in conduction was complicated by electrocardiographic signs suggestive of left ventricular hypertrophy. There was one case of coarctation of the aorta (not included in our series of cases of incomplete right bundle branch block) in which the QRS interval measured 0.12 second. We suspected that in this instance incomplete right bundle branch block was associated with hypertrophy of the left ventricle. Since both the delay in conduction and the increased thickness of the free wall of the left ventricle would contribute to the duration of the QRS interval, it may be assumed that had the hypertrophy not been present the QRS interval would have been shorter. The electrocardiogram shows significant left axis deviation, and the heart was in the semihorizontal electrocardiographic position. The leads from the right side of the precordium show two R waves of rather small and nearly equal voltage, separated by a very deep S deflection. Those from the left side exhibit abnormally tall R waves and inverted T waves. The leads from the midprecordium display deflections of transitional form. In other words, the pattern is similar to that seen in left ventricular hypertrophy, apart from the evidence of delayed activation of the right ventricle.

INCOMPLETE RIGHT BUNDLE BRANCH BLOCK ASSOCIATED WITH MYOCARDIAL INFARCTION OR WITH PULMONARY EMBOLISM

There were eleven cases in our series in which myocardial infarction had occurred. The sex distribution, types of infarcts, and other data are given in Table V. There is comparatively little difference, with regard to the configuration of the ventricular deflections of the electrocardiogram, between incomplete right bundle branch block associated with infarction and complete right bundle branch block associated with infarction. The latter has been discussed in detail by Rosenbaum and others.[7,9] Posterior infarction is recognized by the characteristic changes which it produces in Leads II, III, and V_F. Anteroseptal infarcts abolish the primary R wave in the leads from the right side of the pre-

cordium, but the R′ wave is unusually large in these leads because of the reduction of the opposing left ventricular forces incident to the infarction.

There were two cases in which incomplete right bundle branch block was associated with pulmonary embolism. They are mentioned here for the sake of completeness. These cases will be discussed in detail in a subsequent article.

TABLE V. INCOMPLETE RIGHT BUNDLE BRANCH BLOCK AND MYOCARDIAL INFARCTION

	CERTAIN	PROBABLE
Number		
Males	7	3
Females	1	0
Total	8	3
Average age		
Males	51.6	54.3
Females	59.0	—
Anteroseptal infarct	4	0
Extensive anterior infarct	2	0
Small anterior infarct	1	0
Posterior infarct	1	3
Total	8	3

CORRELATION OF ELECTROCARDIOGRAPHIC AND CLINICAL DATA

Table VI gives the age and sex incidence of incomplete right bundle branch block in our series of cases. It will be noted that the incidence is relatively high in the first decade of life. This is obviously due to the frequency of this conduction defect in congenital heart disease. In the second decade the number of cases is smaller, but thereafter it rises gradually, and the greatest frequency occurs in the fourth, fifth, and sixth decades. There is a preponderance of males over females in the ratio of approximately 3:1.

TABLE VI. INCIDENCE ACCORDING TO DECADES

DECADE	MALES	FEMALES	TOTAL
First	10	1	11
Second	3	3	6
Third	8	4	12
Fourth	18	4	22
Fifth	8	5	13
Sixth	13	8	21
Seventh	9	0	9
Eighth	2	1	3
Totals	71	26	97

Number of cases, 96. Lowest age, 19 months. Average age in females, 41.7 years.
Highest age, 79 years. Average age, 40.8 years. Average age in males, 39.9 years.

Table IV gives the distribution with respect to clinical diagnosis, sex, and age of the patients included in the first four groups. This table has been referred to previously in connection with the discussion of incomplete right bundle branch block associated with right ventricular hypertrophy.

It is interesting to note that twenty of the patients showed no evidence of heart disease. In eight additional instances a diagnosis of possible heart disease, and in four more a diagnosis of potential heart disease was made. There were also three cases of essential hypertension in which evidence of cardiac involvement was not elicited. Consequently, there were in all, thirty-one cases in which a definite diagnosis of heart disease could not be made. It is, therefore, hazardous to make a clinical diagnosis of heart disease on the basis of the electrocardiographic findings alone in cases in which the only demonstrable abnormality is incomplete right bundle branch block. On the other hand, the remaining patients had serious heart disease. There were forty-seven with lesions involving the right and thirteen with lesions involving the left side of this organ.

DISCUSSION AND CONCLUSIONS

Since most of our material has been discussed as it has been presented, there is little need for further emphasis on the great majority of points, except to indicate what we consider the criteria necessary for diagnosis.

Incomplete right bundle branch block should be suspected in every case in which there is a relatively broad S wave in Lead I, especially if the QRS interval is longer than in the average normal electrocardiogram. In our cases of incomplete right bundle branch block the QRS interval ranged from 0.08 to 0.115 second.

The presence of a primary and a secondary R wave or a prominent late R wave in Lead V_R is relatively common in cases of incomplete right bundle branch block, but is also frequent when this conduction defect is not present and is not a reliable sign.

The presence of an early R deflection and a late R′ deflection in the leads from the right side of the precordium, especially if both deflections are present in both Lead V_1 and Lead V_E, is diagnostic. If suggestive changes are present in Lead V_1, or in Leads V_1 and V_2, it is advisable to take additional leads from the right side of the chest (V_{r3} and V_{r4}) or to carry out an even more extensive exploration of the heart field in order to confirm the diagnosis.

When right ventricular hypertrophy and incomplete right bundle branch block are associated, there is, in addition to the changes described, a very tall R′ deflection in the leads from the right side of the precordium. This deflection usually exceeds 10 mm. in height. The leads from the left side of the precordium often show rather small R deflections and deep S waves. However, electrocardiograms representing this combination may exhibit a variety of patterns. Four of these have been described.

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VARIABILITY OF THE ELECTROCARDIOGRAM IN NORMAL YOUNG MEN

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INTRODUCTION

IN THE proper clinical interpretation of electrocardiograms, quantitative criteria of normality are essential, but the values generally used have been arrived at without adequate sampling and detailed statistical analysis. Recently, new data on larger groups of persons have shown that the ranges for many electrocardiographic items in apparently normal persons are greater than had been supposed.[1,2] The diagnosis of such marked pathologic changes as intraventricular block, infarcts, or advanced degrees of preponderance is not called in question, but it is clear that progress in the use of electrocardiography for the evaluation of less extreme abnormalities requires a quantitative approach based on exactly defined standards. Such an approach should take into account not only the differences between individuals but also the fluctuations within individuals. The day-to-day variability of the electrocardiographic complexes is the focus of the present study. This aspect is especially important for a more precise interpretation of borderline electrocardiograms. In addition, the lability of the electrocardiographic complexes as characterized by the size of the day-to-day fluctuations may constitute a new criterion of abnormality, even when the fluctuations occur within the so-called normal limits.

In a thorough search of the literature we failed to find any data on day-to-day variability of the electrocardiogram except an early communication by Lewis.[3] At that time the electrocardiogram was taken with the patient in a sitting position, and many items are not exactly comparable with later material. Lewis,[3,a] while recognizing that the electrocardiographic complexes exhibit considerable differences among healthy individuals, considered the electrocardiogram as essentially constant for a given individual and suggested that it might be adopted as a means of individual identification. He did not analyze the material statistically.

The absence of data on intraindividual variability is surprising in view of the widespread clinical use of electrocardiography. This absence might be explained by

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the present use of the normal range limits as criteria, which implies that the knowledge of intraindividual variability within the normal range is irrelevant for clinical interpretation; and by the tradition, since Einthoven and Lewis, of regarding the electrocardiogram in "normal" subjects as practically constant. Both concepts are basically incorrect.

Knowledge of intraindividual variability is essential for the effective use of serial electrocardiography in patients. Such a dramatic development as healing of a myocardial infarct will probably overshadow completely the magnitude of intraindividual variability, but comparatively minor changes are often interpreted as improvement or deterioration. This cannot be safely done without knowledge of the amount of variation to be expected by "chance" alone in repeated electrocardiograms.

In the present communication, data on the consistency of electrocardiographic complexes in a comparatively small but well-controlled group will be given, together with an analysis of the various sources of variability.

METHOD

Three standard and three chest leads (CF_1, CF_2, and CF_4) were taken on eleven occasions in the basal condition on each of twelve subjects. The location for the placement of the chest electrode was marked by intracutaneous dye injection. The repeated tests were made at intervals of three to eleven days. The whole experimental period was about two months. The dye spots were visible throughout this period. Simultaneously with the electrocardiogram, the heart sounds were recorded during arrested respiration. The interval from the first to the second heart sound was measured as the duration of mechanical systole (systole). In addition, the following intervals were measured: R-R, P-R, QRS, and Q-T. The R-R interval, Q-T interval, and duration of mechanical systole were averaged from five beats, usually in Lead II. The value K, obtained by dividing through $\sqrt{\text{R-R}}$, was calculated both for Q-T, (K_{QT}), and for the duration of mechanical systole ($K_{systole}$).

The difference between the longest and shortest R-R interval in any given electrocardiogram was used as a criterion of arrhythmia (ΔMax.-Min. R-R). The amplitudes of the P waves, the QRS complex, RS-T segments, and T waves were measured in all leads in terms of standardized millimeters, 10 mm. equalling 1 millivolt. In addition to the standard deflection incorporated in the electrocardiograph (Sanborn), an external calibration source was applied.

The axis of QRS and the axis of T were calculated by the use of Dieuaide's procedure. Since the same subjects were tested repeatedly, the usual clinical method for estimation of the over-all magnitude of the QRS complex as the sum of the amplitudes in Leads I, II, and III (Σ_{QRS}), appeared to be sufficient. A similar procedure was used for the T waves (Σ_T). The quotient R/S was calculated for CF_1, CF_2, and CF_4.

The subjects were twelve healthy young men, between 20 and 30 years of age. They received a thorough physical examination before the start of the

experiments. In addition to the clinical routine examination, the response to exercise, heat exposure, and vertical position was tested and found to be normal. Their diet and daily routine during the experimental period was known; major emotional, physical, or nutritional interference during the experimental period could be excluded.

Statistical Procedures.—The methods of statistical analysis used here have been presented in detail previously.[4] The essential task is to determine the portion of the variability of measured electrocardiographic complexes which can be attributed to differences between individuals, day-to-day physiological fluctuation in the electrocardiographic functions, and the error of measurement.

Variation in the electrocardiographic complexes, determined for n individuals on k days, can be expressed in terms of differences arising from three sources: (1) The difference between a value (Y_{ID}), obtained for a given individual (I) on a given day (D), and the mean of all values obtained for the given individual ($Y_{ID} - \overline{Y}_I$). (2) The difference between Y_{ID} and the mean ($\overline{Y}_D$) of the values obtained for all the individuals on a given day ($Y_{ID} - \overline{Y}_D$). (3) The difference between Y_{ID} and a predicted value, $\hat{Y}_{ID}$; i. e. ($Y_{ID} - \hat{Y}_{ID}$). The latter value is based on the grand mean of the determinations on all the individuals on all the days ($\overline{Y}$), the difference between an individual's mean and the grand mean, ($\overline{Y}_I - \overline{Y}$), and the difference between a day's mean and the grand mean, ($\overline{Y}_D - \overline{Y}$); $\hat{Y}_{ID} = \overline{Y} + (\overline{Y}_I - \overline{Y}) + (\overline{Y}_D - \overline{Y})$.

The sums of squared differences, divided by the appropriate "degrees of freedom," are referred to as variances (or "mean squares"). Using the symbols defined, we obtain three variances:

Variance "within days," V_{wD}, indicating the magnitude of the subject-to-subject (interindividual) variation;

$$(1) \quad V_{wD} = \frac{\sum^{nk} (Y_{ID} - \overline{Y}_D)^2}{k\,(n-1)}$$

Variance "within individuals," V_{wI}, representing the magnitude of day-to-day (intraindividual) variation:

$$(2) \quad V_{wI} = \frac{\sum^{nk} (Y_{ID} - \overline{Y}_I)^2}{n\,(k-1)}$$

"Random" variance, V_R, measuring the "random" variation in the scores:

$$(3) \quad V_R = \frac{\sum^{nk} (Y_{ID} - \hat{Y}_{ID})^2}{(n-1)\,(k-1)}$$

The formulas (1) to (3) indicate the theoretical derivation of the variances. In carrying out the actual computations the procedures can be greatly simplified (see Brozek and Alexander[4]).

In evaluating the day-to-day fluctuations in the scores obtained in repeated determinations, the intraindividual variance (V_{wI}) is to be compared with the interindividual variance (variance "within days," V_{wD}).

We may use either a percentage expression:

$$(4) \quad \%\ V_{wI} = \frac{100\,V_{wI}}{V_{wD}} \quad or$$

relate the two values in the form of a coefficient of day-to-day consistency:

$$(5) \quad r'_c = 1 - \frac{V_{wI}}{V_{wD}} \quad .$$

In cases where V_{wI} is significantly larger than V_R, as indicated by the ratio V_{wI}/V_R, the random variance must be used as the measure of the chance variation in the scores. Again, it may be related to V_{wD} in the form of a percentage:

$$(6) \quad \%\ V_R = \frac{100\,V_R}{V_{wD}} \quad , or$$

of a coefficient of consistency:

$$(7) \quad r_c = 1 - \frac{V_R}{V_{wD}}$$

Using the percentage relationship, complete absence of consistency would be indicated by 100 and complete consistency would be indicated by zero. With the variances expressed in terms of a coefficient of consistency, a value of 0.0 indicates complete absence of consistency and a value of 1.0 complete consistency.

So far, the variance within individuals (V_{wI}) has been considered as a uniform source of variability. However, it may be assumed that V_{wI} consists of two parts: (1) the variation due to true day-to-day changes in the electrocardiographic characteristics, estimated as the corrected variance within individuals, *corr.* V_{wI}; (2) the variation due to the error in measuring the records, determined as V_{wM}, the variance within measurements. We assume further that these two variances are additive:

$$(8) \quad V_{wI} = corr.\ V_{wI} + V_{wM}.$$

In order to separate these two sources of intraindividual variation, the electrocardiographic records obtained from the group on one day were independently remeasured three times at intervals of several weeks. All measurements were made by the same person, who had had considerable experience in this task. In computation, V_{wM} is obtained in the same way as V_{wI}, except that it is based on repeated measurements of the same set of records rather than on electrocardiographic determinations made on different days.

TABLE I. MEANS, STANDARD DEVIATIONS (INTERINDIVIDUAL, INTRAINDIVIDUAL, AND ERROR OF MEASUREMENT), AND 90 PER CENT RANGE OF ELECTROCARDIOGRAPHIC ITEMS; LIMB LEADS: ELEVEN REPETITIONS IN TWELVE SUBJECTS

	MEAN	INTERINDIVIDUAL		INTRAINDIVIDUAL		ERROR OF MEASUREMENT		ACCEPTED NORMAL LIMITS
		S.D.	90% RANGE (±)	S.D.	90% RANGE (±)	S.D.	90% RANGE (±)	
Intervals, in 1/100 sec.								
1. R-R	106.9	13.23	21.8	8.59	14.10	0.288	0.474	60 to 100
2. ΔMax.-Min. R-R	8.9	6.90	11.3	5.40	8.90	0.736	1.210	
3. P-R	14.7	2.33	3.8	0.854	1.40	0.612	1.010	12 to 21
4. QRS	7.2	1.31	2.2	0.400	0.66	0.354	0.582	6 to 10
5. K_{QT}	0.394	0.021	0.035	0.015	0.025	0.007	0.012	0.34 to 0.43*
6. $K_{syst.}$	0.326	0.017	0.028	0.011	0.018	0.005	0.008	
Amplitudes, in mm. (1 mm. = 0.1 mv.)								
1. P_2	1.04	0.243	0.40	0.141	0.23	.050	.082	0.3 to 2.5†
2. R_1	5.05	1.98	3.30	0.548	0.90	.097	.160	1.5 to 14†
3. R_2	12.81	4.28	7.00	0.640	1.10	.130	.214	4.0 to 23†
4. R_3	8.97	5.26	8.70	0.825	1.40	.224	.368	1.0 to 20†
5. Σ_{QRS}	29.16	8.73	14.40	1.490	2.50	.329	.541	
6. RS-T_1	0.11	0.17	0.28	0.152	0.25	.110	.181	−0.5 to 2.0‡
7. RS-T_2	0.11	0.20	0.32	0.182	0.30	.084	.138	−0.5 to 2.0‡
8. RS-T_3	0.14	0.24	0.39	0.155	0.25	.100	.164	−1.0 to 2.0‡
9. T_1	2.92	0.91	1.50	0.387	0.64	.089	.146	0.4 to 5.0†
10. T_2	3.83	1.79	2.90	0.439	0.72	.110	.181	0.1 to 6.5†
11. T_3	1.51	1.14	1.90	0.443	0.73	.114	.188	−1.3 to 4.3†
12. Σ_T	8.25	3.27	5.40	0.814	1.30	.158	.260	
Axis								
1. QRS axis°	69.20	16.52	27.20	6.560	10.80	1.740	2.860	
2. T axis°	40.00	19.57	32.20	9.990	16.40	3.330	5.480	

*Shipley and Hallaran[8]
†Wilson[5]
‡Katz and co-workers[9]

The variance ratios provide a satisfactory measure for comparing the consistency of different electrocardiographic items. By their very nature the ratios are abstract numbers. It is useful to supplement them with measures of consistency expressed in the units (time or voltage) in which the items are actually measured. Standard deviations (the square roots of the variances) serve this purpose.

RESULTS

Standard Deviations as Measures of the Variability of Electrocardiographic Items.—The variability of electrocardiographic items, as characterized by the interindividual, intraindividual, and error-of-measurement standard deviations, is indicated in Tables I (limb leads) and II (chest leads). In addition, the range for the various items was calculated on the basis of 90 per cent expectancy. For the purpose of condensation, only the values of P_2 are given as representative for the P wave. Also, the Q waves and S waves in the limb leads were omitted; they were absent or very small in the majority of our subjects.

TABLE II. MEANS, STANDARD DEVIATIONS (INTERINDIVIDUAL, INTRAINDIVIDUAL, AND ERROR OF MEASUREMENT), AND 90 PER CENT RANGE OF ELECTROCARDIOGRAPHIC ITEMS; CHEST LEADS: ELEVEN REPETITIONS IN TWELVE SUBJECTS

AMPLITUDES (MM.)	MEAN	INTERINDIVIDUAL		INTRAINDIVIDUAL		ERROR OF MEASUREMENT	
		S.D.	90% RANGE (±)	S.D.	90% RANGE (±)	S.D.	90% RANGE (±)
1. $R\text{-}CF_1$	2.14	0.42	0.70	0.27	0.44	.091	.150
2. $R\text{-}CF_2$	6.14	2.44	4.00	0.58	0.96	.327	.538
3. $R\text{-}CF_4$	13.01	7.23	11.90	1.60	2.60	.371	.616
4. $S\text{-}CF_1$	16.68	5.87	9.70	1.31	2.20	.406	.668
5. $S\text{-}CF_2$	24.88	9.15	15.10	2.27	3.70	.514	.845
6. $S\text{-}CF_4$	5.57	3.69	6.10	1.30	2.10	.500	.822
7. $RS\text{-}T\text{-}CF_1$	0.20	0.35	0.57	0.19	0.31	.170	.280
8. $RS\text{-}T\text{-}CF_2$	1.17	0.60	0.98	0.44	0.73	.522	.859
9. $RS\text{-}T\text{-}CF_4$	0.71	0.56	0.92	0.35	0.58	.432	.711
10. $T\text{-}CF_1$	−3.06	1.41	2.30	0.57	0.93	.228	.375
11. $T\text{-}CF_2$	6.82	1.94	3.20	0.84	1.40	.268	.441
12. $T\text{-}CF_4$	7.29	2.01	3.30	0.86	1.40	.359	.591
13. $R/S\text{-}CF_1$	0.15	0.09	0.14	0.02	0.03	.008	.013
14. $R/S\text{-}CF_2$	0.29	0.18	0.29	0.05	0.09	.017	.028
15. $R/S\text{-}CF_4$	4.55	5.73	9.40	3.05	5.00	.982	1.620

The variation within individuals is smaller than the variation between individuals, as would be expected for almost any physiologic function; but it is by no means negligible. The variation due to error of measurement obviously plays only a minor role in general. In this section we are primarily

concerned with the day-to-day (intraindividual) variation of repeated electrocardiograms. It may be noted that the daily variability of the R wave in the chest leads is definitely larger than in the limb leads; the 90 per cent range for R in CF_4 (mean, 13.01 mm.) is ± 2.6 mm.; that for R_2 (mean, 12.81 mm.), ± 1.1 millimeters. The daily variability of the quotient R/S is small for CF_1 and CF_2, while it is enormous in CF_4. The variability of the RS-T segment is larger in the chest leads than in the limb leads. Also, the variability of the T wave is quite large; for instance, for T in CF_2 the 90 per cent range of daily variation is from 8.2 to 5.4 millimeters.

In order to make possible a comparison of the intraindividual variation in different electrocardiographic items, the standard deviations or the calculated 90 per cent range may be expressed in some cases as percentages of the mean. Such a procedure is used at times, but it is valid only when the biologic range starts from zero and goes up to a well-defined upper limit. This is not the case for many electrocardiographic characteristics.

A better procedure is to relate the intraindividual variability to the differences between clinically "normal" individuals, expressed as the range of commonly accepted normal limits. These limits are shown in the last column of Table I. No such normal limits are given for the chest leads (Table II) because the norms are less adequate. For illustration, the 90 per cent range of intraindividual variability in percentage of the accepted normal range for the P-R interval is 31.0 per cent; for the QRS interval, 33.0 per cent; for the amplitude of the R wave in Lead II, 11.6 per cent; for the RS-T segment in Lead II, 24.0 per cent; and for the amplitude of the T wave in Lead II, 21.9 per cent.

Statistically, the "normal ranges" are less satisfactory criteria of individual differences than the standard deviations. As these latter are simply the square roots of the variances, in the next section we shall deal directly with them.

Variances and Variance Ratios.—Tables III and IV show the variances (intraindividual variance, V_{wI}; random variance, V_R; and interindividual or "within days" variance, V_{wD}) and the derived consistency coefficients for the various items in limb leads (Table III) and chest leads (Table IV). The ratio of V_{wI} and V_R for all electrocardiographic measurements is very close to 1.00. Consequently, it makes practically no difference which of the two variances is used for calculation of the consistency.

It can be seen that the consistency of the R wave in repeated measurements is high compared to that of the T wave. The amplitudes of R and T in Lead II have a higher degree of consistency than in Lead I or III; probably this reflects the effect of axis variability. The consistency of both the QRS and the T axis is poorer than that of the corresponding amplitudes. The poorer consistency of R in CF_1 and of S in CF_4, compared to the R and S waves in the

TABLE III. VARIANCES AND THE DERIVED CONSISTENCY MEASURES EXPRESSED AS PERCENTAGES ($100\ V_{wI}/V_{wD}$, $100\ V_R/V_{wD}$), AND COEFFICIENTS OF CONSISTENCY ($r'_c = 1 - V_{wI}/V_{wD}$; $r_c = 1 - V_R/V_{wD}$); LIMB LEADS: ELEVEN REPETITIONS IN TWELVE SUBJECTS

	V_{wI}	V_R	V_{wD}	V_{wI}/V_R	$\frac{100\ V_{wI}}{V_{wD}}$	$\frac{100\ V_R}{V_{wD}}$	r'_c	r_c
Intervals								
1. R-R	73.75	75.85	175.07	0.972	42.1	43.3	.579	.567
2. ΔMax-Min R-R	29.18	30.64	47.56	0.952	61.4	64.4	.386	.356
3. P-R	0.73	0.66	5.45	1.11	13.4	12.1	.866	.879
4. QRS	0.16	0.16	1.72	1.00	9.3	9.3	.907	.907
5. K_{QT}	.00023	.00024	.00045	0.954	51.1	53.3	.486	.461
6. $K_{syst.}$	.00013	.00012	.00029	1.03	44.8	41.4	.553	.568
Amplitudes								
1. P_2	0.020	0.021	0.059	0.952	33.9	35.6	.661	.644
2. R_1	0.30	0.30	3.91	1.00	7.7	7.7	.923	.923
3. R_2	0.41	0.38	18.29	1.08	2.2	2.1	.978	.979
4. R_3	0.68	0.64	27.65	1.06	2.5	2.3	.975	.977
5. Σ_{QRS}	2.23	2.13	76.22	1.05	2.9	2.8	.971	.972
6. RS-T_1	0.023	0.024	0.029	0.958	79.3	82.8	.207	.172
7. RS-T_2	0.033	0.033	0.039	1.00	84.6	84.6	.154	.154
8. RS-T_3	0.024	0.023	0.055	1.04	43.6	41.8	.564	.582
9. T_1	0.150	0.153	0.819	0.980	18.3	18.7	.817	.813
10. T_2	0.193	0.189	3.21	1.02	6.0	5.9	.940	.941
11. T_3	0.196	0.192	1.30	1.02	15.1	14.8	.846	.854
12. Σ_T	0.663	0.639	10.70	1.04	6.2	6.0	.938	.940
Axis								
1. QRS axis	43.05	43.11	272.83	.999	15.8	15.8	.842	.842
2. T axis	99.79	103.48	382.94	.964	26.1	27.0	.739	.730

TABLE IV. VARIANCES AND THE DERIVED CONSISTENCY CHARACTERISTICS EXPRESSED AS PERCENTAGES $\left(\frac{100\ V_{wI}}{V_{wD}};\ \frac{100\ V_R}{V_{wD}}\right)$ AND COEFFICIENTS OF CONSISTENCY $\left(r'_c = 1 - \frac{V_{wI}}{V_{wD}};\ r_c = 1 - \frac{V_R}{V_{wD}}\right)$; CHEST LEADS: ELEVEN REPETITIONS IN TWELVE SUBJECTS

AMPLITUDES	V_{wI}	V_R	V_{wD}	$\frac{V_{wI}}{V_R}$	$\frac{100\ V_{wI}}{V_{wD}}$	$\frac{100\ V_R}{V_{wD}}$	r'_c	r_c
1. R-CF_1	0.071	0.068	0.178	1.04	39.9	38.2	.601	.618
2. R-CF_2	0.339	0.332	5.97	1.02	5.7	5.6	.943	.945
3. R-CF_4	2.56	2.28	52.25	1.12	4.9	4.4	.951	.956
4. S-CF_1	1.71	1.64	34.44	1.04	5.0	4.8	.950	.952
5. S-CF_2	5.15	5.02	83.80	1.03	6.1	6.0	.939	.940
6. S-CF_4	1.70	1.70	13.61	1.00	12.5	12.5	.875	.875
7. RS-T-CF_1	0.036	0.037	0.122	0.973	29.5	30.3	.705	.697
8. RS-T-CF_2	0.195	0.201	0.356	0.970	54.8	56.5	.452	.435
9. RS-T-CF_4	0.124	0.125	0.310	0.992	40.0	40.3	.600	.597
10. T-CF_1	0.320	0.302	1.99	1.06	16.1	15.2	.839	.849
11. T-CF_2	0.706	0.696	3.76	1.02	18.8	18.5	.811	.814
12. T-CF_4	0.735	0.786	4.02	0.935	18.3	19.6	.816	.803
13. R/S-CF_1	0.000422	0.000429	0.00743	0.984	5.7	5.8	.943	.942
14. R/S-CF_2	0.00278	0.00286	0.0313	0.972	8.9	9.1	.911	.909
15. R/S-CF_4	9.31	9.61	32.88	0.969	28.3	29.2	.717	.708

other two chest leads, may be due to the smaller amplitude and the consequently greater inaccuracy of measurement. For a convenient survey, the various electrocardiographic items are grouped according to the degree of consistency in Table V.

TABLE V. ELECTROCARDIOGRAPHIC ITEMS, GROUPED ACCORDING TO DEGREE OF CONSISTENCY AS CHARACTERIZED BY r'c

CONSISTENCY	r'c	ITEMS
Very high	>0.9	QRS int.; R_1; R_2; R_3; Σ_{QRS}; T_1; T_2; Σ_T; R-CF_2; R-CF_4; S-CF_1; S-CF_2; R/S-CF_1; R/S-CF_2
High	0.89–0.80	P-R int.; QRS axis; S-CF_4; T-CF_1; T-CF_2; T-CF_4; T_3
Moderate	0.79–0.70	T axis; RS-T-CF_1; R/S-CF_4
Low	0.69–0.60	P_2; R-CF_1; RS-T-CF_4
Very low	<0.60	R-R int.; Δmax-min R-R; K_{QT}; $K_{Syst.}$; RS-T_1; RS-T_2; RS-T_3; RS-T-CF_2

As far as we are aware, the only published material on repeated electrocardiographic determinations is that of Lewis.[3] Table VI shows the comparison of the Minnesota series and Lewis' series. In general, the consistency values are strikingly similar, but most items show a somewhat better consistency in the Minnesota material. It is possible that better physiologic standardization was a contributing factor.

Correction of the Consistency Measures for Homogeneity of the Sample.— The variance "within days," V_{wD}, is the best available estimate of the magnitude of the differences between individuals in the population from which the given sample of subjects was drawn. When we deal with small samples of subjects, highly homogeneous with respect not only to age and sex but also to over-all physical "fitness," the value V_{wD} will tend to be smaller than for more heterogeneous samples, and the apparent consistency of the electrocardiographic items will be low.

We tested this effect by substituting for V_{wD} a value obtained on a larger sample drawn from the same population as our smaller sample. The latter value was obtained under standard conditions on a group of thirty-six men. In addition, we calculated the day-to-day consistency in our material using the data on the variation between individuals in Wilson's[5] material of 104 cases and Graybiel and McFarland's[1] material of 1,000 cases.

Table VII shows the intraindividual variances obtained in the present group of twelve subjects (first column), the interindividual variances (standard deviations squared) of the larger samples (second column), and the corrected consistency indices. No such corrections could be made for the chest leads. Comparison of Table VII with Table III shows an appreciable improvement in consistency for the following items: R-R interval, P_2, RS-T_1, RS-T_2, RS-T_3,

TABLE VI. COMPARISON OF CONSISTENCY CHARACTERISTICS IN LEWIS' AND IN THE PRESENT (MINNESOTA) MATERIAL FOR SELECTED ELECTROCARDIOGRAPHIC ITEMS

ITEMS	SOURCE	NUMBER OF SUBJECTS	NUMBER OF REPETITIONS	V_{wI}	V_R	V_{wD}	$\frac{V_{wI}}{V_R}$	$\frac{100\ V_{wI}}{V_{wD}}$	$\frac{100\ V_R}{V_{wD}}$	r'_e	r_e
P_2	Lewis	16	2	0.024	0.025	0.052	0.960	46.2	48.1	.538	.519
	Minn.	12	11	0.020	0.021	0.059	0.952	33.9	35.6	.661	.644
R_1	Lewis	16	2	0.078	0.065	1.89	1.20	4.13	3.44	.959	.966
	Minn.	12	11	0.30	0.30	3.91	1.00	7.7	7.7	.923	.923
R_2	Lewis	16	2	0.461	0.403	4.00	1.14	11.53	10.08	.885	.899
	Minn.	12	11	0.41	0.38	18.29	1.08	2.2	2.1	.978	.979
R_3	Lewis	16	2	1.281	1.365	9.09	0.938	14.1	15.0	.859	.850
	Minn.	12	11	0.68	0.64	27.65	1.06	2.5	2.3	.975	.977
T_1	Lewis	16	2	0.128	0.130	0.535	0.985	23.9	24.3	.761	.757
	Minn.	12	11	0.150	0.153	0.819	0.980	18.3	18.7	.817	.813
T_2	Lewis	16	2	0.301	0.321	1.112	0.938	27.1	28.9	.729	.711
	Minn.	12	11	0.193	0.189	3.21	1.02	6.0	5.9	.940	.941
T_3	Lewis	16	2	0.214	0.228	0.472	0.939	45.3	48.3	.547	.517
	Minn.	12	11	0.196	0.192	1.30	1.02	15.1	14.8	.846	.854
R-R	Lewis	16	2	99.81	105.60	273.03	0.945	36.6	38.7	.634	.613
	Minn.	12	11	73.75	75.85	175.07	0.972	42.1	43.3	.579	.567
P-R	Lewis	16	2	0.375	0.400	2.30	0.938	16.3	17.4	.837	.826
	Minn.	12	11	0.73	0.66	5.45	1.11	13.4	12.1	.866	.879

QRS axis, and T axis. Most of these items are in the low or poor consistency group (Table V). Most of the items with high consistency were not improved.

TABLE VII. THE CONSISTENCY CHARACTERISTICS OBTAINED BY USING THE BEST AVAILABLE ESTIMATE OF THE VARIATION OF A GIVEN ELECTROCARDIOGRAPHIC VARIABLE IN THE NORMAL POPULATION

	V_{wI}	SD^2	$\frac{100\ V_{wI}}{SD^2}$	CORR. r'_c
Intervals				
1. R-R	73.75	246.18*	29.96	.700
2. ΔMax-Min R-R	29.18	49.00†	59.55	.404
3. P-R	0.73	(4.84)*	(15.08)	(.849)
4. QRS	0.16	(1.00)*	(16.00)	(.840)
5. K_{QT}	0.00023	(.00031)†	(74.2)	(.258)
6. K_{systol}	0.00013	(.00025)†	(52.0)	(.480)
Amplitudes				
1. P_2	0.020	0.152*	13.16	.868
2. R_1	0.30	6.6*	4.55	.955
3. R_2	0.41	(15.1)*	2.72	.973
4. R_3	0.68	(17.6)*	3.86	.961
5. Σ_{QRS}	2.23	(60.06)†	(3.71)	(.963)
6. RS-T_1	0.023	0.0399*	57.6	.424
7. RS-T_2	0.033	0.104*	31.7	.683
8. RS-T_3	0.024	0.096*	25.0	.750
9. T_1	0.150	(0.781)*	(19.21)	(.808)
10. T_2	0.193	(1.4)*	(13.79)	(.862)
11. T_3	0.196			
12. Σ_T	0.663	(6.30)†	(10.52)	(.895)
Axis				
1. QRS Axis	43.05	542.89*	7.93	.921
2. T Axis	99.79	552.72†	18.05	.819

Parentheses were placed around values for those electrocardiographic characteristics for which $SD^2 < V_{wD}$.

* = Graybiel and associates.[1]

† = Control values in the Minnesota Starvation Experiment.

Correction of the Consistency Measures for the Error of Measurement.— Three independent measurements were made on one electrocardiogram from each of the twelve subjects. The data yielded a two-way table, similar in structure to the data obtained by actually making separate electrocardiographic determinations on different days. This body of data was analyzed by the techniques of the analysis of variance. Tables VIII and IX show the corrected intraindividual variances obtained by using the values of V_{wM}, the variance "within measurements," for correction, and the corrected consistency indices. The last column of Tables VIII and IX shows the proportion of the error of measurement, V_{wM}, in terms of the percentage of uncorrected V_{wI}.

The error of the measurement itself is the major source of the total day-to-day variation (>50 per cent of V_{wI}) in the following items: P-R and QRS interval, RS-T segments in Leads I, CF_2, and CF_4; it is an appreciable source of variation (20 to 50 per cent of V_{wI}) for $K_{Q\text{-}T}$, RS-T_2, RS-T_3, and R in CF_2.

TABLE VIII. VARIANCE OF THE DERIVED CONSISTENCY CHARACTERISTICS OBTAINED BY CORRECTING THE INTRAINDIVIDUAL VARIANCE FOR ERRORS OF MEASUREMENT (V_{wM}): CORR. $V_{wI} = (V_{wI} - V_{wM})$: LIMB LEADS

	V_{wM}	V_{wI}	V_{wD}	CORR. $V_{wI} = (V_{wI} - V_{wM})$	$\frac{100 \text{ CORR. } V_{wI}}{V_{wD}}$	CORRECTED r'_c	$\frac{100\ V_{wM}}{V_{wI}}$
Intervals							
1. R-R	.083	73.75	175.07	73.67	42.1	.579	0.11
2. ΔMax-Min R-R	.542	29.18	47.56	28.64	60.2	.398	1.86
3. P-R	.375	0.73	5.45	0.36	6.61	.934	51.3
4. QRS	.125	0.16	1.72	0.035	2.03	.980	78.1
5. K_{QT}	.000054	0.00023	0.00045	0.000176	39.11	.609	23.5
6. $K_{syst.}$	.000024	0.00013	0.00029	0.000105	36.55	.634	18.5
Amplitudes							
1. P_2	.0025	0.020	0.059	0.018	30.5	.695	12.5
2. R_1	.0096	0.30	3.91	0.29	7.4	.926	3.2
3. R_2	.017	0.41	18.29	0.39	2.1	.979	4.1
4. R_3	.050	0.68	27.65	0.63	2.3	.977	7.4
5. Σ_{QRS}	.108	2.23	76.22	2.12	2.8	.972	4.8
6. RS-T_1	.012	0.023	0.029	0.011	37.9	.621	52.2
7. RS-T_2	.007	0.033	0.039	0.026	66.7	.333	21.2
8. RS-T_3	.010	0.024	0.055	0.014	25.5	.745	41.7
9. T_1	.0079	0.150	0.819	0.142	17.3	.827	5.3
10. T_2	.012	0.193	3.21	0.181	5.6	.944	6.2
11. T_3	.013	0.196	1.30	0.183	14.1	.859	6.6
12. Σ_T	.025	0.663	10.70	0.638	6.0	.940	3.8
Axis							
1. QRS Axis	3.04	43.05	272.83	40.01	14.7	.853	7.1
2. T Axis	11.08	99.79	382.94	88.71	23.2	.768	11.1

TABLE IX. VARIANCE OF THE DERIVED CONSISTENCY CHARACTERISTICS OBTAINED BY CORRECTING THE INTRAINDIVIDUAL VARIANCE FOR ERRORS OF MEASUREMENT: CORR. $V_{wI} = (V_{wI} - V_{wM})$; CHEST LEADS

ITEMS	V_{wM}	V_{wI}	V_{wD}	CORR. V_{wI}	$\frac{100 \text{ CORR. } V_{wI}}{V_{wD}}$	r'_e	$\frac{100\ V_{wM}}{V_{wI}}$
1. R-CF_1	.0083	0.071	0.178	0.063	35.4	.646	11.7
2. R-CF_2	.107	0.339	5.97	0.232	3.9	.961	31.6
3. R-CF_4	.138	2.56	52.25	2.42	4.6	.954	5.4
4. S-CF_1	.165	1.71	34.44	1.55	4.5	.955	9.6
5. S-CF_2	.264	5.15	83.80	4.89	5.8	.942	5.1
6. S-CF_4	.250	1.70	13.61	1.45	10.7	.893	14.7
7. RS-T-CF_1	.029	0.036	0.122	0.007	5.7	.943	80.6
8. RS-T-CF_2	.273	0.195	0.356				
9. RS-T-CF_4	.187	0.124	0.310				
10. T-CF_1	.052	0.320	1.99	0.268	13.47	.865	16.3
11. T-CF_2	.072	0.706	3.76	0.634	16.86	.831	10.2
12. T-CF_4	.129	0.735	4.02	0.606	15.07	.849	17.6
13. R/S-CF_1	.000063	0.000422	0.00743	0.000359	4.83	.952	14.9
14. R/S-CF_2	.000296	0.00278	0.0313	0.00248	7.92	.921	10.6
15. R/S-CF_4	.964	9.31	32.88	8.35	25.4	.746	10.3

The improvement of consistency obtained by eliminating the error of measurements can be seen by comparison of Tables III and VIII, or IV and IX. After the correction, the poor-consistency items (r'_c <0.6) are reduced from eight to four.

DISCUSSION

From the point of view of repeatability, there are no absolute criteria for judging whether a given electrocardiographic item is or is not satisfactory. The grading of consistency from very high to very low in Table V is essentially arbitrary, a matter of judgment and agreement. The meaning of the measures of consistency may be clarified by considering the term $\%V_{wi}$, defined in Formula 4 as the ratio of the intraindividual ("within individuals") to the interindividual ("within days") variance. When the value $\%V_{wi}$ approaches zero, the particular electrocardiographic item is highly characteristic of the individual. When the intraindividual variance approaches 100 per cent of the interindividual variance, the electrocardiographic item is not a stable individual characteristic. A low consistency may be due either to large day-to-day fluctuations in the particular function (and, in part, to the inaccuracies of the measurements) or to the compression of the range of the individual differences, that is, an extreme homogeneity of the sample. The present sample of twelve subjects may appear small. However, there is evidence that the interindividual variability in the greater part of the electrocardiographic items was actually not much different from the variability in much larger samples, including Graybiel and McFarland's material (1,000 subjects).

For clinical electrocardiography, the determination of the intraindividual standard deviations and the 90 per cent range limits are probably the most important results of the present study. Variations within this range are entirely within the limits of variability to be expected by "chance," that is, resulting from a complex of uncontrolled factors, and should not be interpreted as improvement or deterioration in patients. It seems safe to assume that the intraindividual variability of patients will not be smaller than that of normal subjects. The agreement as to the variability of repeated determinations in the present material and in that of Lewis is surprisingly good, in spite of the fact that the samples were obtained on different continents and the determinations were separated by an interval of thirty-six years. This gives assurance that these data may be used for evaluating the significance of changes produced by stress or therapy.

The variability was studied over a comparatively short period of two months; consequently, the data cannot be used for the prediction of variations during considerably longer intervals. It should be pointed out that the repeated determinations were in the basal state. Under less rigorously standardized conditions, the intraindividual variability would increase. For example, it has been shown that such factors of everyday life as eating a meal of moderate size may change significantly the electrocardiogram of patients as well as of normal individuals.[6,7] Also, in subjects differing from those used in the present study in age, physical

activity, emotional status, and so forth, the range of day-to-day variations may be different. Further information on this point is needed.

Proper consideration of intraindividual variability is especially important for the interpretation of electrocardiograms on the borderline of clinical normality. If the mean of repeated determinations of an electrocardiographic item is outside the limits of clinical normality, the electrocardiogram should be interpreted as abnormal, even when the values fall occasionally within the normal limits. Conversely, if the mean falls within the normal limits, the occasional values beyond these limits should not be regarded as indicators of abnormality. It is evident that for a more precise interpretation of borderline cases serial electrocardiograms are necessary.

SUMMARY

Electrocardiograms were taken on twelve normal young men in the basal state on eleven different occasions over a period of two months. Three standard and three chest leads were used, and thirty-five electrocardiographic items were measured. In addition, one set of electrocardiograms was measured by the same assistant on three different occasions.

The amount of variation contributed by interindividual differences, by day-to-day physiologic fluctuation, and by inaccuracy in measuring the records was determined statistically.

The ratio of the intraindividual to the interindividual variance was used as the criterion of the consistency of repeated electrocardiographic determinations. Out of thirty-five electrocardiographic items, the consistency was very high (consistency coefficient $\geq$ 0.90) in fourteen, high (0.89 to 0.80) in seven, moderate (0.79 to 0.70) in three, low (0.69 to 0.60) in three, and very low ($<$0.60) in eight.

The consistency measures were corrected for the homogeneity of the sample of subjects by substituting estimates of interindividual variance based on much larger samples, and for the inaccuracy of measurement of the electrocardiographic records.

The 90 per cent expectancy range of intraindividual variability was calculated. These data may be applied for interpretation of borderline electrocardiograms and for evaluation of degrees of deterioration or improvement in serial electrocardiograms.

We wish to express our thanks and appreciation to Miss A. Bjella, Mr. A. Butler, Mr. W. Steinberger, and Mr. W. Thompson for their assistance in this study.

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A STUDY OF THE Q-T INTERVAL IN RHEUMATIC FEVER

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RECENT studies by Ashman[1] and by Taran and Szilagyi[2] have indicated that during the course of acute rheumatic fever the Q-T interval may become prolonged and constitute an important sign of rheumatic activity. Because of this, we decided to reinvestigate this subject. We studied the electrocardiograms of 100 young patients in Lincoln Hospital up to the age of 20 years. Of these, fifty patients had active rheumatic fever, twenty-five patients were in the quiescent stage, and, as a control group, twenty-five additional cases were studied by us. All patients had sinus rhythm. The only medication the patients received was salicylates, unless otherwise noted.

METHOD

Electrocardiographic studies were done on all 100 patients. Lead II was used for the measurement of the Q-T interval. Ten successive cycles were measured and the average obtained. Serial electrocardiograms were taken on all the active cases, and, in addition, the patients' clinical courses were followed, with frequent blood counts, erythrocyte sedimentation rates, and temperature (rectal) and pulse studies.

We used the following method of analyzing variations in the Q-T interval. Since the Q-T interval varies with the ventricular rate, more or less complicated formulas must be used. One of the simplest is that devised by Bazett, namely, $Q\text{-}T = k\sqrt{R\text{-}R}$, where k is a constant and $R\text{-}R$ is the interval between two successive R waves.[3] Bazett pointed out that k is the same in men and children, but longer in women, and described the constant as 0.37 for men and children and 0.40 for women. We used the constant 0.40 for all of our cases. This value corresponds to that used by Taran and Szilagyi.

Thus, in order to calculate accurately whether a measured Q-T interval is prolonged, it must be compared with the ideal Q-T interval determined from Bazett's formula. The relation between the measured Q-T interval and the ideal Q-T interval can then be described as a percentage or a ratio. For example, let us suppose there is a tracing in which the heart rate is 75, the Q-T interval is 0.40 second, and the R-R interval is 0.80 second. From Bazett's formula, the ideal Q-T interval is 0.358 second. The measured Q-T interval is, however,

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TABLE I. ELECTROCARDIOGRAPHIC AND CLINICAL DATA IN FIFTY CASES OF ACTIVE RHEUMATIC FEVER

ELECTROCARDIOGRAPHIC DATA								CLINICAL DATA			
CASE	AGE	SEX	ECG DATE*	RATE	Q-T	R-R	Q-T$_R$†	TEMP.‡	E.S.R.	W.B.C.	REMARKS§ (° F. throughout)
1	8	F	4/14/44	83	0.34	0.76	0.98	98.2	56	17,900	Initial temperature of 104°, with gradual decline to normal; polyarthritis; polyarthritis one year before
			4/27/44	67	0.36	0.90	0.95	99.4	34	—	
			5/17/44	61.5	0.38	0.98	0.96	99.0	34	—	
			6/20/44	85	0.34	0.70	1.02	100.0	28	6,200	
			7/17/44	77	0.34	0.78	0.96	98.2	20	—	
	11		10/ 8/46	110	0.34	0.54	1.16	100.0	95	13,150	Temperature never exceeded 101°; polyarthritis, chest pain, dyspnea; ECG showed elevated RS-T segments in all leads, and there was clinical evidence of pericarditis
			10/11/46	92	0.36	0.64	1.13	99.0	—	—	
			10/29/46	61.5	0.42	0.98	1.07	99.2	45	7,100	
2	8	M	7/ 3/46	93	0.36	0.64	1.13	99.6	76	18,600	Temperature never exceeded 100°; sore throat, arthralgia, anorexia; had polyarthritis one year before
			7/10/46	93	0.34	0.64	1.07	100.0	—	—	
			7/22/46	100	0.36	0.60	1.16	99.6	19	10,400	
3	15	M	5/21/46	110	0.30	0.54	1.03	100.6	85	8,400	Temperature never exceeded 100.6°; polyarthritis and erythema multiforme; had polyarthritis at age of 10
			5/31/46	87	0.32	0.68	0.97	98.6	95	—	
			6/24/46	115	0.30	0.52	1.04	98.6	75	—	
4	19	M	5/10/46	70	0.40	0.90	1.06	100.2	40	—	Temperature never exceeded 101°; polyarthritis
			5/14/46	68.6	0.40	0.88	1.07	98.6	—	6,100	
			5/17/46	68.6	0.40	0.88	1.07	98.6	—	—	
5	15	F	5/ 7/46	70.5	0.34	0.84	0.93	102.6	120	12,000	Initial temperature of 103.4°, with gradual decline to normal; polyarthritis
			5/15/46	70.5	0.36	0.84	0.98	99.0	120	—	
			5/27/46	75	0.36	0.80	1.01	98.6	75	7,000	
6	11	F	7/10/46	135	0.26	0.44	0.98	99.8	78	13,400	Temperature never exceeded 100.2°; polyarthritis and dyspnea; went on to develop congestive heart failure and was ditigalized shortly before death
			7/22/46	130	0.30	0.46	1.11	99.6	38	—	
			7/30/46	130	0.28	0.46	1.04	98.6	36	—	
			8/ 2/46*	125	0.32	0.48	1.16	99.0	—	—	
7	11	M	5/21/46	105	0.32	0.56	1.07	100.0	80	13,150	Temperature never exceeded 100.4°; polyarthritis
			5/27/46	115	0.32	0.52	1.11	99.4	59	—	
			6/12/46	83	0.36	0.72	1.07	99.0	22	6,100	

8	13	F	1/ 2/45	70.5	0.36	0.84	0.98	99.4	117	17,450	Initial temperature of 104°, with gradual decline to normal; polyarthritis; abdominal pains
			1/18/45	81	0.34	0.74	0.99	99.8	68	—	
9	2½	M	12/19/42	135	0.24	0.44	0.91	100.2	120	16,000	Temperature never exceeded 100.6°; abdominal pains, chills, anorexia; developed clinical and roentgenologic evidence of pericarditis and pericardial effusion
			12/22/42	150	0.26	0.40	1.03	100.0	—	—	
			12/24/42	120	0.24	0.50	0.85	100.4	—	—	
			1/ 4/43	120	0.22	0.50	0.78	100.2	90	10,000	
			1/11/43	115	0.24	0.52	0.83	100.0	—	—	
			1/25/43	115	0.28	0.52	0.98	99.0	—	10,800	
			2/ 8/43	105	0.28	0.56	0.94	99.4	60	13,000	
			3/ 8/43	115	0.26	0.52	0.90	99.0	8	10,000	
10	4½	F	12/ 5/44	125	0.28	0.48	1.01	102.0	110	21,200	Initial temperature of 103.2°, with gradual decline to normal; arthralgia, sore throat
			12/18/44	115	0.28	0.52	0.97	99.8	50	—	
			1/20/45	93	0.32	0.64	1.00	99.0	4	6,050	
11	8	M	11/ 1/45	125	0.28	0.48	1.01	103.0	50	10,200	Initial temperature of 104°, with gradual decline to normal; polyarthritis
			11/21/45	91	0.32	0.66	0.98	99.0	23	—	
			12/ 6/45	68.6	0.36	0.88	0.96	99.8	41	12,300	
12	11	M	5/22/44	125	0.26	0.48	0.94	103.8	44	18,000	Initial temperature of 104.2°, with gradual decline to normal; polyarthritis
			5/29/44	77	0.36	0.76	1.04	99.0	99	—	
			6/ 9/44	72	0.36	0.72	1.07	99.0	49	—	
			6/27/44	87	0.34	0.68	1.04	99.0	11	9,200	
			7/ 3/44	93	0.34	0.66	1.05	99.0	—	—	
	12½		4/28/45	69	0.38	0.90	1.01	99.0	55	14,450	Initial temperature of 101°, with gradual decline to normal; anorexia, vague abdominal pains
13	14½	M	3/11/46	83	0.34	0.72	1.01	99.2	52	8,900	Initial temperature of 102°, with gradual decline to normal; polyarthritis
			3/19/46	96	0.32	0.62	1.02	99.0	12	—	
	14½		4/ 5/46	70.5	0.36	0.84	0.98	98.6	45	—	Initial temperature of 101°, with rapid decline to normal; admitted because of fever at home
14	9½	F	3/30/44	100	0.32	0.60	1.04	99.2	125	21,750	Temperature never exceeded 99.4°; polyarthritis
			4/10/44	70.5	0.38	0.84	1.04	99.0	13	14,200	
			4/27/44	93	0.34	0.64	1.07	99.0	14	12,000	
	12		2/15/47	105	0.32	0.56	1.07	102.8	97	16,900	Initial temperature of 103.2°, with gradual decline to normal; polyarthritis; large pulmonary conus on x-ray of chest
			3/10/47	110	0.28	0.54	0.95	102.2	63	—	

TABLE I. ELECTROCARDIOGRAPHIC AND CLINICAL DATA IN FIFTY CASES OF ACTIVE RHEUMATIC FEVER—(CONTINUED)

ELECTROCARDIOGRAPHIC DATA								CLINICAL DATA			
CASE	AGE	SEX	ECG DATE*	RATE	Q-T	R-R	Q-T_R†	TEMP.‡	E.S.R.	W.B.C.	REMARKS§ (° F. throughout)
	12		3/28/47	105	0.36	0.56	1.21	99.0	60	9,700	Normal temperature throughout course; polyarthritis
15	12	M	8/ 1/46 8/12/46	77 55	0.38 0.36	0.78 0.88	1.08 0.97	101.0 98.6	120 97	6,800 —	Initial temperature of 101°, with gradual decline to normal; polyarthralgia, polyuria, anorexia, malaise
	12½		11/26/46	87	0.36	0.68	1.09	98.6	42	—	Normal temperature throughout course; chorea
16	5	F	2/18/47 3/ 6/47 3/18/47 3/22/47*	125 115 142 115	0.28 0.28 0.28 0.28	0.48 0.52 0.42 0.52	1.02 0.97 1.08 0.97	100.0 99.0 100.2 99.4	124 104 88 —	19,500 — — —	Temperature never exceeded 100.6°; polyarthritis, precordial pain; went on to develop congestive heart failure and was digitalized shortly before death
17	4	M	2/21/47 3/12/47	103 125	0.32 0.32	0.58 0.48	1.05 1.16	102.0 100.0	108 61	22,000 —	Initial temperature of 103°, with gradual decline to normal; polyarthritis and abdominal pain
18	16	M	2/24/47	79	0.30	0.76	0.86	101.0	90	17,700	Initial temperature of 101°, with rapid decline to normal; polyarthritis
19	8	F	7/15/41 8/ 8/41 8/19/41	105 93 100	0.30 0.32 0.32	0.56 0.64 0.60	1.01 1.00 1.03	99.2 100.0 99.0	25 18 19	12,000 9,200 —	Temperature never exceeded 100.4°; arthralgia
20	5	M	1/29/47 2/18/47	125 100	0.28 0.34	0.48 0.60	1.02 1.11	99.4 98.2	95 11	10,500 —	Initial temperature of 101°, with gradual decline to normal; arthralgia, anorexia
21	13	M	7/ 7/46 8/15/46	87 83	0.40 0.36	0.68 0.72	1.21 1.07	101.0 99.8	103 60	14,000 8,650	Initial temperature of 103.4°, with gradual decline to normal; polyarthritis
22	20	F	4/25/46 5/ 2/46 5/16/46 5/27/46 5/29/46 6/24/46	115 105 110 93 96 93	0.32 0.34 0.34 0.34 0.36 0.34	0.52 0.56 0.54 0.64 0.62 0.64	1.11 1.14 1.14 1.07 1.15 1.07	99.8 99.0 98.6 100.0 99.0 99.0	135 122 51 45 28 30	9,900 — — — — —	Temperature never exceeded 100°; precordial sticking pain, arthralgia, dyspnea, and anorexia; polyarthritis three years earlier; treated for syphilis at the age of 19

23	13	F	6/18/46 7/ 3/46	70.5 48	0.44 0.40	0.84 1.18	1.20 0.93	100.0 99.0	118 85	12,000 —	Temperature never exceeded 100.5°; polyarthritis
24	7	F	7/19/46 7/31/46	110 90	0.30 0.32	0.54 0.66	1.03 0.98	100.2 99.8	140 25	13,700 —	Initial temperature of 102.6°, with gradual decline to normal; polyarthritis, epistaxis, chills
25	5	M	6/26/46 7/ 2/46	93 105	0.32 0.30	0.62 0.56	1.01 1.01	99.0 99.6	118 110	12,950 —	Initial temperature of 101°, with gradual decline to normal; polyarthritis, pharyngitis
26	7	F	2/15/45 2/19/45 3/ 8/45	115 105 90	0.30 0.32 0.36	0.52 0.56 0.66	1.04 1.07 1.11	99.8 99.0 99.0	115 — 25	22,500 — —	Initial temperature of 101°, with gradual decline to normal; abdominal pain; developed clinical and roentgenologic evidence of pericardial and right pleural effusion
	8		2/ 5/46 2/14/46	85 75	0.36 0.38	0.70 0.80	1.08 1.07	99.0 99.2	92 55	7,400 —	Normal temperature throughout course; chest pain, dyspnea and orthopnea
27	11	F	3/24/45 5/24/45	135 90	0.28 0.34	0.66 0.66	1.06 1.05	102.0 99.0	123 25	14,050 6,800	Initial temperature of 102°, with gradual decline to normal; polyarthritis
	13		11/15/46 11/22/46	90 90	0.32 0.32	0.68 0.72	0.98 0.98	99.0 99.0	52 30	14,150 —	Normal temperature throughout course; dyspnea and hemoptysis; E.H., M.I., and M.S.
28	9	M	4/26/40 5/ 9/40	93 63	0.36 0.36	0.64 0.96	1.13 0.92	102.0 99.2	95 8	8,800 7,700	Initial temperature of 103.2°, with gradual decline to normal; recurrent polyarthritis for three years; E.H., M.I., M.S., and A.I.
	16		7/10/47 7/22/47	97 57	0.30 0.40	0.62 1.04	0.95 0.98	100.0 98.6	56 10	7,400 —	Temperature never exceeded 100°; polyarthritis, E.H., M.I., M.S., A.I., and A.S.; P-R interval: 0.32 and 0.20, respectively
29	6½	M	5/ 5/47 5/23/47	100 83	0.32 0.32	0.46 0.72	1.16 0.94	100.0 99.2	63 18	10,000 —	Initial temperature of 102°, with gradual decline to normal; polyarthritis at 4 and 5 years; headache and polyarthritis
30	10	M	3/25/47 4/ 2/47	125 125	0.32 0.32	0.48 0.48	1.16 1.16	100.0 99.4	33 37	8,200 7,400	Initial temperature of 102.2°, with gradual decline to normal; RHD at 8 years; polyarthritis
31	4	F	1/ 8/47 1/13/47 2/18/47	150 150 97	0.24 0.28 0.32	0.40 0.40 0.60	0.95 1.11 1.04	102.2 100.0 99.2	120 — 58	24,000 — 15,300	Initial temperature of 102.2°, with gradual decline to normal; anorexia, abdominal pain, nausea, vomiting, and convulsions; had clinical evidence of pericarditis

TABLE I. ELECTROCARDIOGRAPHIC AND CLINICAL DATA IN FIFTY CASES OF ACTIVE RHEUMATIC FEVER—(CONTINUED)

ELECTROCARDIOGRAPHIC DATA								CLINICAL DATA			
CASE	AGE	SEX	ECG DATE	RATE	Q-T	R-R	Q-T_R†	TEMP.‡	E.S.R.	W.B.C.	REMARKS§ (° F. throughout)
32	9	F	5/21/47	103	0.28	0.58	0.93	99.0	48	12,200	Temperature never exceeded 100.8°; polyarthritis, erythema nodosum
33	11	M	2/18/47	100	0.28	0.60	0.90	100.0	91	7,600	Initial temperature of 101°, with gradual decline to normal; polyarthritis
34	17	M	5/ 1/47	81	0.34	0.74	0.99	101.0	93	9,600	Initial temperature of 103°, with gradual decline to normal; polyarthritis
35	16	M	1/ 9/47	79	0.36	0.76	1.04	99.0	95	19,600	Initial temperature of 102.6°, with gradual decline to normal; polyarthritis and dyspnea
36	14	M	3/27/47	103	0.32	0.58	1.05	99.0	30	10,300	Initial temperature of 102.4°, with gradual decline to normal; polyarthritis, anorexia
37	3	F	3/ 8/45	135	0.26	0.44	0.98	99.8	130	—	Temperature never exceeded 99.8°; polyarthritis
	5		2/11/47	100	0.32	0.60	1.03	99.2	125	19,950	Temperature normal throughout course; polyarthritis
38	4½	F	5/20/43	110	0.28	0.54	0.95	99.2	12	9,400	Temperature never exceeded 100°; epistaxis and polyarthritis
	5		12/ 8/43	120	0.28	0.50	0.99	100.0	48	6,600	Temperature never exceeded 100°; epistaxis, restlessness
	8		4/ 2/47	103	0.32	0.58	1.06	99.2	73	14,300	Initial temperature of 101°, with gradual decline to normal; epistaxis and polyarthritis
39	4	F	3/ 3/39	125	0.28	0.48	1.01	103.2	94	21,800	Initial temperature of 103.2°, with gradual decline to normal; polyarthritis and dyspnea
40	13	M	1/ 9/47	83	0.42	0.72	1.24	98.6	98	—	Normal temperature throughout course; polyarthritis

41	11	M	9/13/46	83	0.38	0.72	1.13	99.0	49	4,900	Initial temperature of 101°, with gradual decline to normal; polyarthritis; RHD at 9 years of age
	12		4/22/47	93	0.36	0.64	1.13	99.2	40	11,300	Temperature never exceeded 100°; tachycardia, nausea, precordial pain
42	14	F	4/17/47	83	0.36	0.72	1.07	99.0	28	14,600	Temperature never exceeded 100.4.°; polyarthritis
43	11	M	5/14/43 6 26 43	87 60	0.34 0.38	0.68 1.00	1.04 0.95	101.0 99.8	35 8	10,000 —	Initial temperature of 102°, with gradual decline to normal; polyarthritis, nausea, and vomiting
44	11	F	4/18/47	105	0.30	0.56	1.01	99.2	106	10,900	Temperature never exceeded 100°; polyarthritis
45	10	M	5/19/47	81	0.32	0.66	0.98	100.4	88	12,800	Initial temperature of 101°, with gradual decline to normal; polyarthritis
46	5	F	6/23/47	125	0.26	0.44	0.98	100.0	44	8,600	Temperature never exceeded 100°; polyarthritis
47	14	M	1/18/46	93	0.28	0.64	0.87	101.0	90	18,300	Initial temperature of 102°, with gradual decline to normal; long history of colds and epistaxis; polyarthritis
	15		5/ 6/47	103	0.32	0.58	1.05	101.0	94	11,250	Initial temperature of 101.6°, with gradual decline to normal; polyarthritis; M.I., M.S.
48	7	F	5/16/46	77	0.38	0.78	1.16	99.0	125	15,000	Initial temperature of 102°, with gradual decline to normal; polyarthritis, nausea
49	14	F	3/30/46 4/12/46	100 77	0.32 0.36	0.60 0.78	1.03 1.02	99.0 99.0	52 50	8,100 —	Temperature never exceeded 100°; polyarthritis
50	13	F	5/27/47 7/22/47 8/ 8/47	115 71 71	0.30 0.32 0.36	0.52 0.84 0.84	1.03 0.87 0.98	100.2 100.0 99.0	120 52 10	12,300 — —	Initial temperature of 100.4°, with gradual decline to normal; epistaxis and cough; M.I. and M.S. on admission, which gradually disappeared

*Taken just before death and after digitalization.
†Q-T ratio (the ratio of actual to ideal Q-T interval).
‡Maximum temperature on day electrocardiogram was taken. See also *Remarks*.
§E.H., enlarged heart. R.H.D., rheumatic heart disease. M.I., mitral insufficiency. M.S., mitral stenosis. A.S., aortic stenosis. A.I., aortic insufficiency.

0.40 second; this is $\frac{0.400}{0.358}$ greater than normal. Calculating this as a percentage, one obtains the value of 112 per cent. Thus, the measured Q-T interval is 112 per cent of the ideal Q-T interval expected for a ventricular rate of 75. A simpler way of expressing this is to say that the *Q-T ratio*, or $Q\text{-}T_R$, is 1.12. All calculations of the Q-T ratio were made using a nomogram devised by one of us (E. G.[4]).

RESULTS

General Remarks.—Theoretically, a Q-T ratio above 1.0 is abnormal; however, normal controls frequently give values above this. As a basis for our studies, we calculated Q-T ratios from twenty-five normal children and also maximum values of the Q-T ratio from the data compiled by Ashman and Hull.[5] We found that the average normal Q-T ratio is 1.01 in men and children. The maximum normal limit of the Q-T ratio for men and children is 1.08.

The Q-T Interval During Active Rheumatic Fever.—Measurements of the Q-T intervals of our fifty active cases are given in Table I, with clinical and laboratory data.

Our results can be summarized as follows:

1. Only fourteen (28 per cent) of our fifty active cases had Q-T ratios longer than the normal maximum value of 1.08.
2. However, twenty-one (42 per cent) other patients had, at one time or another, a Q-T ratio longer than the average normal value of 1.01.
3. Fifteen patients (30 per cent) with active rheumatic fever never showed a Q-T ratio that even reached the normal average values. In many of these cases, it is true, only one electrocardiogram was taken. But we even observed this when serial electrocardiograms were taken (Cases 5, 8, 10, 11, 13, 16, 27, and second admission of 28).

In a general way, the abnormal Q-T ratio went hand in hand with the clinical state of the patient. For example, in Case 6 the Q-T interval became markedly prolonged just before death. However, marked discrepancies occurred. For example, in Case 9 the Q-T interval remained within normal limits even during an attack of acute pancarditis and pericarditis. Case 1 had normal Q-T intervals during her first admission for polyarthritis, but prolongation of the Q-T interval occurred during her second admission three years later.

No correlation could be made between the Q-T intervals and laboratory data such as erythrocyte sedimentation rate and white blood count.

The Q-T Interval in Quiescent Cases of Rheumatic Fever.—One of the advantages believed to be obtained by measuring the Q-T interval is that this interval should be normal in cases of quiescent rheumatic fever. Study of our twenty-five quiescent cases (Table II) bears this out. None of the patients had a longer Q-T ratio than the maximum normal value of 1.08. However, eight of our patients had Q-T ratios longer than the average Q-T ratio of 1.01. This is in contrast to our twenty-five normal control cases (Table III), where only three had Q-T ratios above 1.01.

TABLE II. ELECTROCARDIOGRAPHIC AND CLINICAL DATA IN TWENTY-FIVE CASES OF QUIESCENT RHEUMATIC FEVER

CASE	AGE	SEX	RATE	Q-T	R-R	Q-T_R*	REMARKS†
1	6	F	100	0.28	0.60	0.99	Acute rheumatic episode six months before
2	6	F	105	0.28	0.56	0.94	Acute rheumatic episode one year before
3	7	M	81	0.32	0.74	0.93	History of an attack of RHD
4	13	F	73	0.32	0.82	0.88	History of an attack of RHD
5	17	M	79	0.34	0.76	0.98	History of an attack of RHD, E.H., and M.I.
6	14	M	79	0.34	0.76	0.98	History of an attack of RHD
7	15	F	110	0.30	0.54	1.03	History of an attack of RHD, M.I., and M.S.
8	10	F	105	0.30	0.56	1.01	History of an attack of RHD
9	15	F	73	0.36	0.82	0.99	History of an attack of RHD
10	15	M	63	0.36	0.96	0.93	Multiple rheumatic episodes: E.H., M.I., M.S., A.I., and A.S.
11	14	M	69	0.34	0.88	0.91	Acute rheumatic episode three years before
12	20	M	65	0.33	0.92	0.86	History of an attack of RHD, E.H., and M.I.
13	14	F	87	0.32	0.68	0.97	Acute rheumatic episode eight years before
14	11	F	100	0.32	0.60	1.03	Chorea two years before
	12		93	0.32	0.64	1.00	Large pulmonary conus and right heart on fluoroscopy
15	11	F	79	0.36	0.76	1.04	Acute rheumatic episode five years before
16	17	F	86	0.32	0.74	0.93	History of dyspnea one year before; M.I. and M.S.
17	15	M	105	0.28	0.56	0.94	History of attacks of RHD; M.I. and M.S.
18	17	F	81	0.34	0.74	0.99	Acute rheumatic episode at the age of 11
19	9	M	100	0.30	0.60	0.97	Acute rheumatic episode one year before
20	9	M	93	0.28	0.64	0.87	Acute rheumatic episode two years before
21	7	F	79	0.32	0.76	0.92	Acute rheumatic episode four months before
22	10	F	85	0.34	0.70	1.02	Acute rheumatic episode three years before
23	13	F	71	0.34	0.84	0.94	Acute rheumatic episode four years before
24	10	F	87	0.32	0.68	0.97	Acute rheumatic episode five months before
25	2½	M	120	0.28	0.50	0.99	Acute rheumatic episode with pericarditis three months before

*Q-T Ratio (the ratio of actual to ideal Q-T interval).

†RHD, rheumatic heart disease; E.H., enlarged heart; M.I., mitral insufficiency; M.S., mitral stenosis; A.I., aortic insufficiency; A. S., aortic stenosis.

TABLE III. ELECTROCARDIOGRAPHIC DATA IN TWENTY-FIVE NORMAL CHILDREN AND YOUNG ADULTS

CASE	AGE	SEX	RATE	Q-T	R-R	Q-T_R*
1	7	F	115	0.28	0.52	0.97
2	16	M	75	0.36	0.80	1.01
3	18	F	83	0.32	0.72	1.00
4	15	F	60	0.41	1.00	1.03
5	14	M	69	0.34	0.88	0.91
6	12	F	87	0.32	0.68	0.97
7	7	M	100	0.28	0.60	0.91
8	20	F	64	0.42	0.98	1.07
9	8	F	87	0.32	0.68	0.97
10	20	M	79	0.34	0.76	0.98
11	14	M	67	0.34	0.90	0.89
12	14	M	63	0.40	0.96	1.03
13	14	F	100	0.30	0.60	0.97
14	9	F	90	0.32	0.66	0.98
15	10	M	87	0.32	0.64	1.00
16	9	F	87	0.28	0.64	0.87
17	15	F	83	0.34	0.72	1.01
18	9	M	83	0.34	0.72	1.01
19	11	F	79	0.32	0.76	0.92
20	5	F	115	0.24	0.52	0.83
21	9	M	97	0.30	0.62	0.97
22	10	F	65	0.32	0.92	0.83
23	4	F	87	0.30	0.68	0.91
24	6	M	110	0.28	0.54	0.95
25	7	F	93	0.31	0.64	0.97

*Q-T Ratio (the ratio of actual to ideal Q-T interval).

DISCUSSION

Our results are somewhat in conflict with those recently reported by Taran and Szilagyi,[2] who found an abnormal Q-T interval in all their cases of active rheumatic fever. They, however, used a different index, namely "a corrected Q-T interval or $Q\text{-}T_C$." The $Q\text{-}T_C$, however, is also based on Bazett's formula, $Q\text{-}T = k\sqrt{R\text{-}R}$. The maximum normal $Q\text{-}T_C$ which they found was 0.405.

Our results can be compared with theirs because a $Q\text{-}T_C$ of 0.405 roughly corresponds to a Q-T ratio of 1.01. Thus, even according to their criteria, 30 per cent of our active cases had normal $Q\text{-}T_C$ values. Part of the discrepancy between their results and ours may be due to the type of cases studied. None of their patients was over 14 years of age, whereas we included patients up to 20 years of age. The exact cause of the prolongation of the Q-T interval that occurs in rheumatic fever is unknown.

CONCLUSIONS

In our study of the Q-T interval in rheumatic fever, as measured by the Q-T ratio, we found that marked prolongation of the Q-T ratio beyond a maximum normal value of 1.08 occurred in only 28 per cent of our cases of active rheumatic fever. However, in 42 per cent more of the active cases, the Q-T ratio was longer than the average normal value of 1.01. Thus, a total of 70 per cent of our active cases had a Q-T ratio longer than average. This is in contrast to the fact that only 12 per cent of our normal control subjects had Q-T ratios above average.

In our quiescent cases of rheumatic fever there were no abnormal Q-T ratios, but 24 per cent had Q-T ratios above average.

Thus, we may conclude the following:

1. During active rheumatic fever, prolongation of the Q-T interval is not invariable but may occur.

2. During the quiescent state, the Q-T interval is within normal.

3. An abnormal Q-T interval in a patient with a history of previous rheumatic fever is a suggestive sign of rheumatic activity.

We wish to thank Dr. Harry Altman, Director of the Pediatric Service at Lincoln Hospital, for his cooperation.

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Clinical Reports

RECOVERY FROM SUBACUTE BACTERIAL ENDOCARDITIS (STREPTOCOCCUS FECALIS)

Report of Two Cases

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THE literature is replete with reports of patients who have been cured of subacute bacterial endocarditis since the advent of penicillin. The vast majority of these patients were, however, infected with *Streptococcus viridans*. The treatment of patients infected with *Streptococcus fecalis* has remained generally unsatisfactory. Isolated reports of cures have been published. Mac Neal[3] cured a patient with subacute bacterial endocarditis who was infected with *S. fecalis* by using Thiobismol, neoarsphenamine, bacteriophage, and penicillin. Hunter[2] treated five patients infected with *S. fecalis*, some with streptomycin alone, and some with streptomycin and penicillin. Four of the five patients were not helped, but one patient was cured. Organisms of the patient cured were sensitive to 3.5 micrograms of streptomycin per cubic centimeter, and therapy consisted of a total of 125 Gm. of streptomycin given over a period of thirty-two days and 4 million units of penicillin given daily for four weeks. This patient was reported to be well ten months after therapy was completed.

Indications are that more of these patients can be cured if sufficient amounts of penicillin are given. We have treated two patients with the disease, both of whom were infected with extremely resistant strains of *S. fecalis*.

The organisms isolated from our patients were identified as *S. fecalis* by Dr. Marcus A. Krupp, head of our clinical laboratory. The organisms were gram-positive cocci which grew in short chains, were not bile-soluble, and grew in 6.5 per cent solution of sodium chloride, as well as in 0.1 per cent methylene blue.

CASE REPORTS

Case 1.—C. G., a 53-year-old white man, was admitted to the Veterans' Administration Hospital at San Francisco on July 26, 1946, for continuance of penicillin therapy for subacute bacterial endocarditis. He had probably been ill for one year previous to his admission, because at that time he noticed that he began to tire quite easily and began to run a low-grade

From the Veterans' Administration Hospital, San Francisco, Calif.

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fever, which was present for a few hours each day. During the next several months he went to a physician, who gave him sulfonamide drugs, and to a chiropractor, who prescribed a low-fat diet and manipulation of the spine. At the end of five to six months of this treatment he felt worse, had lost about fifty pounds in weight, and was beginning to develop dyspnea and ankle edema. On May 8, 1946, his physician sent him to a local hospital, where a diagnosis of subacute bacterial endocarditis was established. *S. fecalis* was identified in his blood culture. He was started on 20,000 units of penicillin every three hours, and his dosage was gradually increased, so that at the end of five weeks he was receiving 800,000 units every three hours. His blood cultures, however, remained positive for *S. fecalis*. He continued to run a low-grade fever and developed petechiae over the arms and legs. On June 21, 1946, he was transferred to the Stanford University Hospital, where sensitivity tests revealed that a concentration of 10 units of penicillin per cubic centimeter of media were required to inhibit his organisms, and it was further determined that 1.5 million units of penicillin every three hours, or 12 million units of penicillin per day, were required to maintain an adequate blood level. His blood penicillin level reached 100 units per cubic centimeter, and this level was probably reached because of the renal lesion the patient had at this time. A blood culture taken after one week of this therapy was sterile. Simultaneously his symptoms began to disappear.

He was transferred to this hospital on July 26, 1946. At that time he was still well nourished and did not appear acutely ill. Abnormal physical findings were limited to the heart and abdomen. The pulse rate was 80 per minute and regular. His heart was not enlarged. A harsh systolic murmur was heard, loudest over the apex, but also heard over the left sternal border. No diastolic murmurs or thrills were present. The blood pressure was 140/80. The spleen was enlarged to one and one-half inches below the left costal margin and the liver was enlarged a similar distance below the right costal margin. No petechiae were seen.

The total red blood cell count was 4 million, with 11 Gm. of hemoglobin. The white blood cell count was 7,400, with a normal differential. Urinalysis showed a small amount of albumin. There were 17 white blood cells per high dry field and 4 red blood cells per high dry field of a centrifuged specimen. An occasional granular cast was seen. A twenty-four hour Addis count showed 360,000 granular casts, 18 million white blood cells, and 164.4 million red blood cells. The total protein excreted in a twenty-four hour urine specimen was 1.6 grams. The blood urea nitrogen was 33.2 mg. per 100 c.c. and the blood creatinine was 2.8 mg. per 100 cubic centimeters. Blood Wassermann and Kahn tests were negative. Electrocardiograms were normal, and x-ray films of the chest confirmed that the heart was not enlarged. The treatment was continued, and the patient received 1.5 million units of amorphous penicillin every three hours, because crystalline penicillin was not available to us at that time. Because of the great pain suffered with these injections, after three days the patient refused to continue with this therapy and stated that he would rather die than take any more injections. Fortunately, we were able to obtain crystalline penicillin at this time, and the treatment was continued on a similar dosage of the crystalline preparation, without further difficulty. This therapy was continued until August 22, at which time the patient had completed sixty days of effective therapy and had received a total of 720 million units of penicillin. At this time penicillin therapy was stopped, and all laboratory tests were essentially normal except for a slight elevation of the sedimentation rate, which remained about 20 mm. per hour, and a trace of albumin in the urine. After the start of his intensive penicillin therapy the patient had no positive blood cultures. He was discharged from the hospital on Nov. 15, 1946, and has been seen every month since that time. His urine continued to show a trace of albumin for about six months after his discharge from the hospital, and then became clear. His blood cultures have been consistently sterile, and at this time the blood count, urinalysis, sedimentation rate, electrocardiogram, and chest x-ray film are well within normal limits. The apical systolic heart murmur is still present, but the spleen and liver can no longer be felt. He has no evidence of infection or cardiac failure. He has worked daily at his regular job as a salesman and has no complaints whatsoever at this time, eighteen months after his discharge from the hospital.

CASE 2.—E. D., a 49-year-old white man, was admitted to the hospital on Jan. 8, 1947, complaining of a painful swollen area on his left temple. In 1933, fourteen years previous to his admission to this hospital, he had an episode of acute urinary retention because of a urethral stricture, the result of an acute gonococcal urethritis which he developed in 1917. In October, 1946, he had a recurrence of acute urinary retention and was admitted to a Naval Hospital. He was told that he had a urethral stricture, and sounds were passed. It was at this time that he developed a round, swollen area on the lateral aspect of the left ankle, which was quite tender, and a low-grade fever. Therapy consisted of hot packs to the ankle and oral sulfadiazine. After ten days of treatment the swelling, pain, and fever completely subsided and he was discharged from the hospital and remained well for two months.

Then four days previous to the patient's admission to this hospital (three months later) he developed a swollen, tender area over the left temple and ran a fever between 101° and 102° F. for the two evenings preceding his admission. He had no other complaints whatsoever. At the time of entry he was well nourished and well developed. He had a fever of 99.6° Fahrenheit. There was a 4.0 by 5.0 cm. raised area on the left temple overlying the left temporal artery, an area which was quite painful to pressure. This lesion was not fluctuant. It was noted that the left temporal artery could be felt pulsating proximal to the lesion, and although the artery could be felt distal to the lesion, no pulsation could be discerned there. The patient's lungs and heart were entirely normal. The pulse rate was 78 per minute and regular. The blood pressure was 114/88. Neither the liver nor the spleen could be felt. The left peroneal artery was occluded. This lesion probably developed in October, 1946. There was a marked similarity between the lesions of the left temporal artery and the left peroneal artery. Pulsation of the branch of the left peroneal artery was present proximal but not distal to the site of the lesion described in the previous hospital entry. Otherwise the physical examination was not remarkable.

His urine showed a faint trace of albumin and 10 to 12 white blood cells per high dry field in a centrifuged specimen. No casts or red blood cells were present. The sedimentation rate was 24 mm. in one hour. The red blood cell count was 4,370,000, with 12 Gm. of hemoglobin. The white blood cell count was 10,000, with 45 per cent segmented cells, 13 per cent nonsegmented cells, 34 per cent lymphocytes, 6 per cent monocytes, and 2 per cent eosinophils. Blood Wassermann and Kahn tests were negative. The electrocardiogram and the chest films were not remarkable.

The patient continued to have a low-grade fever. On Jan. 18, 1947, a biopsy was taken of the left temporal artery at the site of the lesion, as well as of the left peroneal artery at the site of the previous lesion. These sections revealed a diffuse panarteritis of both vessels. No thrombi or organisms were seen. After three weeks of hospitalization the patient's spleen was first felt just below the left costal margin. Repeated examinations of the patient revealed no cardiac disease. Blood cultures, however, showed a heavy growth of *S. fecalis*. On January 21, the organisms were found to be insensitive to a concentration of 20 units of amorphous penicillin per cubic centimeter, but were sensitive to 1.0 unit of streptomycin per cubic centimeter. On February 3, the patient was started on 0.5 Gm. of streptomycin given intramuscularly every three hours. On February 8, the organisms had increased their resistance to a point where they were no longer inhibited by 25 units of streptomycin per cubic centimeter. Streptomycin therapy was therefore stopped, and the patient was started on 0.5 Gm. of sulfadiazine and 0.5 Gm. of sulfathiazole every three hours orally. Retest of the organisms on February 24 showed that they were sensitive to between 1.5 and 2.0 units of crystalline penicillin G per cubic centimeter. Retest of the original organisms showed them also to be sensitive to between 1.5 and 2.0 units of crystalline penicillin G in contrast to the apparently high resistance the organisms showed when tested with amorphous penicillin. On March 20, the patient was started on 2.5 million units of crystalline penicillin every three hours, or 20 million units per day. Between the time of admission and the beginning of this therapy the patient had thirteen successive blood cultures which showed *S. fecalis*. On March 13, the patient suddenly developed pain and redness at the tip of the left fifth finger. The lesion disappeared in a few days. Blood cultures made on March 24 and March 28, about ten weeks after the patient's admission to the hospital, were sterile, but the patient did not

remain afebrile until the first of April. On April 4, three months after admission to this hospital and fifteen days after the start of penicillin therapy, a loud aortic diastolic murmur was heard for the first time, although the patient had been examined daily by members of the house staff and consultants' staff. Blood pressure at that time was 100/60. On April 15, a Grade 2 apical systolic murmur appeared. The laboratory tests remained essentially unchanged except for an eosinophilia, which at times reached 20 per cent. The patient continued to receive penicillin and blood transfusions until May 18, at which time penicillin was stopped. He had received 20 million units of penicillin a day for sixty days, or a total dosage of 1.2 billion units of penicillin.

The patient was discharged from the hospital on May 29, 1947, and was asymptomatic. He has come back to our follow-up clinic every month since his discharge, and has been working daily as an automobile mechanic. His blood count and sedimentation rate have remained normal and his blood cultures have remained sterile. His electrocardiogram reveals no changes. The aortic diastolic murmur persists, as does the apical systolic murmur.

DISCUSSION

The treatment of subacute bacterial endocarditis requires the administration of adequate amounts of a suitable antibiotic to inhibit growth of the causative organisms. It is of the utmost importance, therefore, that the sensitivity of the organisms to the antibiotic be tested in all cases of subacute bacterial endocarditis. We have used penicillin as our antibiotic of choice. The testing of the sensitivity of the organisms has been stressed by Bloomfield[1] and others, but its particular importance when *Streptococcus fecalis* is being dealt with has not been emphasized. When patients with *S. fecalis* infection receive adequate dosages of penicillin, their disease is apparently no harder to cure than the disease of those patients who are infected with the more sensitive *S. viridans*. We have no reason to believe that their sequelae should be different or more severe. We used no agents to blockade the renal excretion of penicillin, although it is conceivable that some patients may require this measure. One of our patients had a renal lesion which in itself contributed to maintaining an extremely high penicillin blood level. Because of the resistance of *S. fecalis*, artificial measures for the blockade of renal excretion of penicillin might otherwise have been required for him.

Because of the pain induced by the administration of amorphous penicillin in the amounts required for these patients, it is imperative to use crystalline penicillin if the intramuscular route, which we consider the most satisfactory, is to be used.

SUMMARY

Two patients suffering from subacute bacterial endocarditis caused by *S. fecalis* have been presented. Because of the insensitivity of this organism to antibiotics now available, massive doses were used. One of these patients received 12 million units of penicillin a day for sixty days, or a total dosage of 720 million units of crystalline penicillin. The other patient received 20 million units a day, or a total dosage of 1.2 billion units. Both of these men are asymptomatic at this time and have shown no clinical or laboratory evidences of recurrence of their disease since their discharge from the hospital.

The organisms of one of the patients were at first quite sensitive to streptomycin, being inhibited by 1 unit of the drug per cubic centimeter of medium. After the patient had received 4.0 Gm. of streptomycin intramuscularly for forty-eight hours, however, the organisms were resistant to 25 units of streptomycin per cubic centimeter of medium. It thus became impossible to reach effective therapy by the use of streptomycin for this patient.

It is of importance to note that this same patient's organisms were insensitive to 20 units of amorphous penicillin per cubic centimeter but were sensitive to between 1.5 and 2.0 units of crystalline penicillin. Whether this was due to deterioration of the amorphous penicillin or whether a substandard drug was used is not known. In view of the above findings, however, we believe that crystalline penicillin should be used not only because of its more constant potency but also because of the fact that it is less painful to administer.

It is interesting to note that the one patient developed his initial arteritis six months before he showed any clinical evidence of cardiac involvement. In spite of careful daily search, the valvular lesion did not become evident until the fifteenth day after penicillin therapy had been started.

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DELAYED DEATH FOLLOWING CONTUSION OF THE HEART

Report of a Case

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THE symptoms and consequences of nonpenetrating traumatic injuries to the heart have not always been recognized and have been the subject of much dispute in the recent past. Interest in these lesions was reawakened in this country when Beck,[1,2] Bright,[1] Moritz,[3,4] and Atkins[3] published the results of their observations on such injuries and of experiments conducted to reproduce them. They explored their mode of origin, symptoms, the anatomic and histologic changes produced by them, and possible methods of treatment.

In their historical review of the literature from 1850 on, Beck and Bright[1] collected twelve cases in which the patients had survived the trauma and thirteen in which they had died of myocardial failure. Stern,[5] in his exhaustive chapters on traumatic diseases of the heart, amplified this list and added other cases from his own experience. The studies made by these authors formed an important step in the acceptance of the diagnosis of contusion of the heart as a complex of clinical symptoms and disturbances following the traumatic impact. However, all the authors cited emphasized the necessity of amplifying the literature by additional reports of cases thoroughly examined and, if possible, observed from the time of trauma through post-mortem examination. It is for this purpose that the following case history and observations are presented.

CASE REPORT

A 20-year-old Negro man was struck by an automobile and knocked to the street by the impact. He was conveyed to the hospital, where an x-ray film of the thorax did not reveal any fracture of the bony parts. Therefore, after the administration of first aid for bruised ribs, he was released. The following day he consulted his family physician because of pains in the left side of his chest. He was treated for bruises. Only slight abrasions of the skin were noted. The patient did not remain in bed, but since he felt rather weak and tired, he did not return to work.

Eight days after the injury the patient still did not feel well. A physician found a slightly elevated temperature (under 100° F.) and an accelerated pulse rate. He was treated for a cold and advised to remain in bed for a few days. He seemed to improve after a few days of rest, but two weeks after the accident he complained suddenly of a severe pain in the left side of his chest. He was observed to be alert, but weak and perspiring. His pulse rate was markedly accelerated; his temperature less than 99° Fahrenheit. Because of the rapid collapse, he was sent to a hospital immediately. He was pronounced dead on arrival at the hospital, and was taken to the Cuyahoga County Morgue, where the author performed the post-mortem examination.

From the Office of the Coroner, Cuyahoga County, Ohio.

The history which has been cited is a compilation of the information elicited from the police, the physician who rendered first aid, the family physician, and the doctor who ordered the patient to go to the hospital.

Excerpts From the Autopsy Findings.—There is a linear, whitish, depigmented scar of the skin over the fifth and sixth ribs on the left side, in the parasternal line. This scar measures 3.0 cm. in length and 6.0 to 7.0 mm. in width. Vestiges of hemorrhages are seen in the perichondrium of the cartilages of the sixth to tenth left ribs close to their insertion at the sternum. Cartilages of the sixth, seventh, and eighth ribs on the left side show slightly depressed fractures close to their insertion at the sternal border.

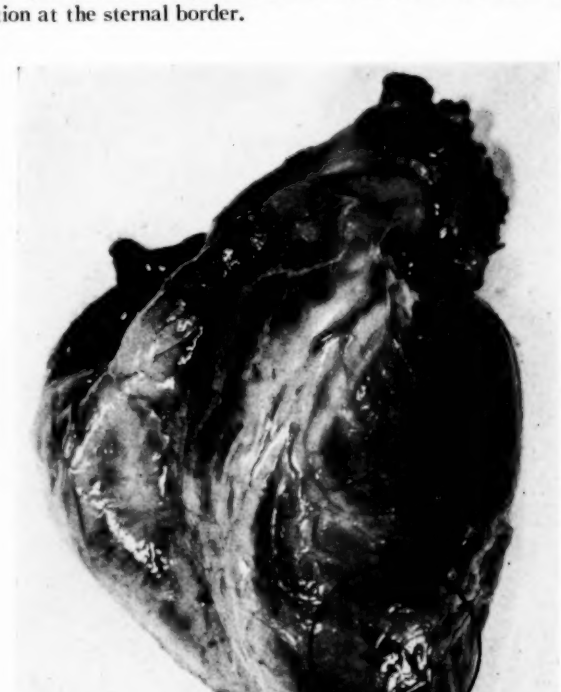

Fig. 1.—Anterior aspect of heart showing area of contusion of wall of left ventricle.

There are about 50 c.c. of yellowish fluid in the pleural sac. The heart is of medium size and weighs 250 grams; the right ventricle measures 8.0 cm. in length and the left ventricle, 10 cm. in length. There are a number of subepicardial ecchymoses crossing and surrounding a grayish, pale area of about 2.0 cm. in diameter at the anterior side of the left ventricle, near its tip. A subepicardial hemorrhage 8.0 mm. in diameter is seen at the lateral side of the left ventricle approximately 3.0 cm. below its base. Several small ecchymoses can be seen at the posterior side of the left ventricle (Fig. 1). The anterior wall of the left ventricle in this area bulges slightly, and its thickness is reduced to about 5.0 mm., of which, on cross section, 2.0 to 3.0 mm. show a brownish discoloration such as is seen after a previous hemorrhage, as described by Moritz and Atkins.[3]

Further findings reveal patent and elastic coronary arteries and aorta, pulmonary edema, venous congestion of spleen and liver, and cerebral edema.

This case was brought to the attention of Dr. Claude S. Beck, and acknowledgement is hereby made of appreciation and indebtedness to Dr. Beck and Mr. Wolfe for their assistance in the completion of this study. At Dr. Beck's direction, Mr. Wolfe injected both coronary arteries with a barium mass prior to the opening of the heart. X-ray films made before and also after dissection showed a striking decrease in both the number and size of the capillaries in the area at the anterior side of the left ventricle (Fig. 2).

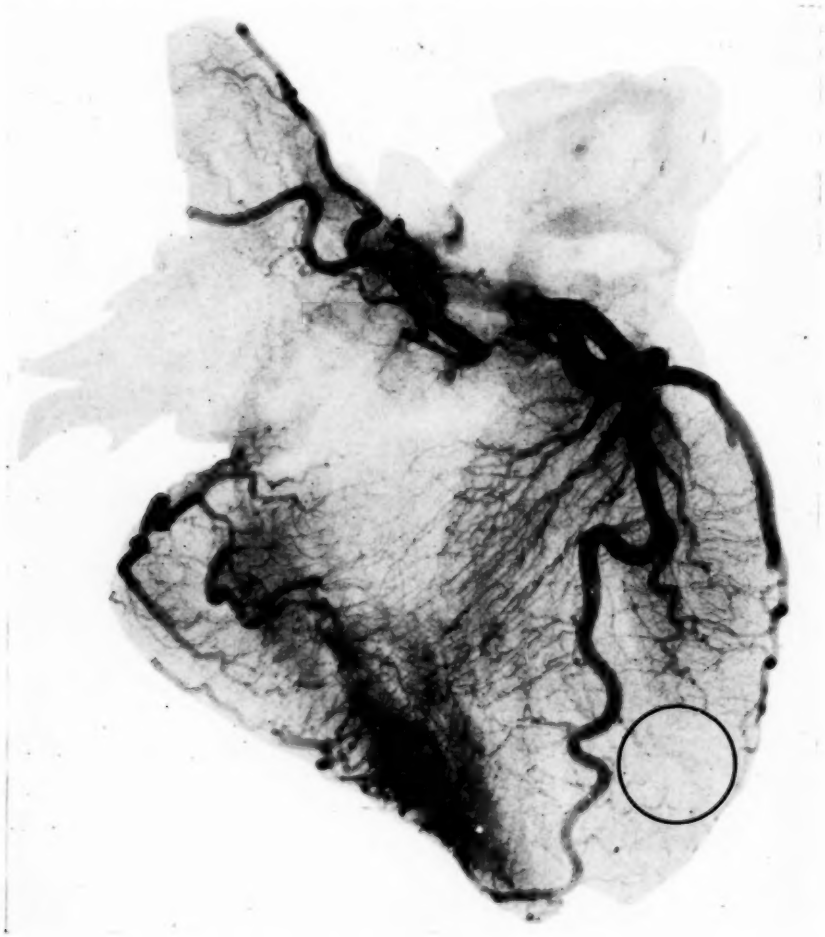

Fig. 2.—X-ray film of the heart showing the decrease in number and size of capillaries at the site of the contusion near the apex of the left ventricle. Coronary arteries were injected with a barium paste.

The microscopic examinations of the grayish, pale area were less impressive. They revealed a somewhat thickened epicardium infiltrated with white cells. The capillaries in the subepicardial layers and the adjoining musculature were more or less collapsed. The patent ones were surrounded by a plasmalike material and by white cells. The loosened interstitial tissue between

the muscle fibers likewise was filled with plasmalike material and white cells, most of which were mononuclear. There was marked fragmentation of muscle fibers (Fig. 3). The microscopic picture from areas of the heart not affected was not abnormal.

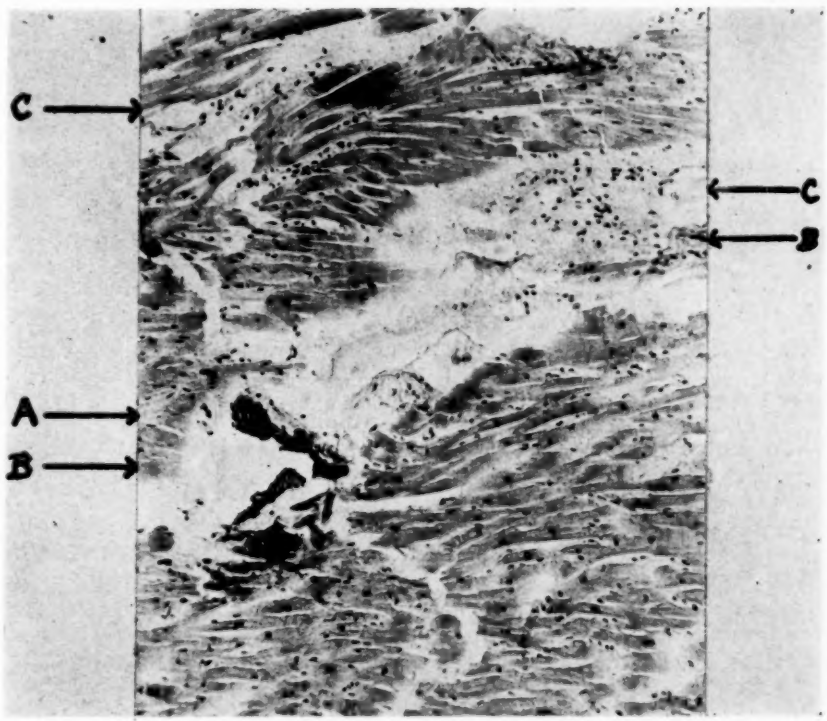

Fig. 3.—Microscopic section of area of contusion. *A*, injected capillary; *B*, collapsed capillaries; *C*, round cells in the interstitial plasmalike material. In various areas throughout the picture fragmentation of the muscle fibers is visible.

DISCUSSION

The gross picture of this heart and the microscopic findings in the area of contusion bear a striking resemblance to the descriptions given by Beck and Bright[1] and Moritz and Atkins.[3,4] The case history is similar to a case described by Beck.[2] The fact that death occurred in the second week seems to bear on Beck's[2] conclusion: "If the patient survives the first nine hours after the accident, his chances of living through the first week are somewhat better than his chances of going through the second week. After the second week it would seem that the area of contusion becomes stronger through the development of scar tissue."

The present case was complicated by the presence of the fractured costal cartilages, which may have caused further aggravation. Unfortunately, there

were no electrocardiograms taken to confirm Beck's assertion that death may occur as a result of ventricular fibrillation in such cases of contusion of the heart.

It is estimated that between 93 and 95 per cent of all cases of contusion of the heart which are not followed by immediate death due to rupture or injuries to other vital organs (as in steering wheel injuries) may heal without further manifest symptoms or noticeable consequences, and may escape clinical recognition.[6,7]

If, following the advice of Beck[1] and Stern,[5] every injury to the chest with or without manifest fractures were treated with the possibility of heart contusion in mind, many lives might be saved. The treatment should include bed rest. Repeated electrocardiograms should be taken.

SUMMARY

Contusions of the heart probably occur more frequently than is commonly supposed, and may easily be overlooked. This is indicated by the foregoing report of a case in which a post-mortem examination was made of a 20-year-old man with a history of an accident which at the time was not considered to be serious.

Symptoms displayed several days later were believed to be due to a common cold. Only a few hours before death the patient developed terrific precordial pain and died enroute to the hospital. Autopsy revealed fractures of cartilages of the left costal arch and typical signs of contusion of the heart.

The treatment and origin of contusions of the heart are mentioned.

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Abstracts and Reviews

Selected Abstracts

Edwards, E. A.: Nail Changes in Functional and Organic Arterial Disease. New England J. Med. **239**:362 (Sept.), 1948.

The author presents the results of a study of the nails in vasospastic and organic vascular disorders. In such conditions as the cold, stiff, splinted extremity, Raynaud's disease, and scleroderma, the proximal nail fold (the part of the nail plate overlain by skin) becomes very thin and merges gradually into the translucent cuticle. The latter membrane does not end abruptly at its distal or free edge, as it does normally, and is greatly widened. This condition has been termed "pterygium." The changes appear to be an accurate herald of coming scleroderma. They are not seen in the presence of purely organic vascular disorders but appear to be limited to those conditions in which there are vasospastic reflexes mediated through the sympathetic nervous system. Sympathectomy promptly does away with the lesion. In three or four weeks after the operation, the nail fold has become full and the new cuticle is seen growing in its normal sharply delineated manner.

Severe ischemia, due to organic arterial vascular disease, gives rise to a distortion of the growth of the nail plate (nail proper). The linear growth is retarded to the extent that the nail may not have to be trimmed for months or years. The nail plate may increase in thickness, becoming heavy and rough as a result of transverse or eccentrically placed parallel ridging. The nail plate is darkened. The distortion of nail growth may take the form of a claw nail (onychogryposis).

An increase of blood supply is signalled by a return of the roughened nail to normal growth, with a rapid distal displacement of the old misshapen nail by a new, more normal portion. The contrast between the old diseased nail and the newer portion serves as a striking indication of the improvement of the circulation and is clinically useful in evaluating the benefit of therapy.

ABRAMSON.

Friedfeld, L., Marcus, H. R., and Vorzimer, J. J.: Aminophyllin Determination of Circulation Time. New York State J. Med. **48**:2047 (Sept. 15), 1948.

Substances for measuring the circulation time, which produce an end point measurable by objective means, frequently have limited use because of undesirable side reactions. It seemed logical, therefore, to utilize the well-known effect of aminophyllin, which causes a suddenly deepened and rapid respiration, for the determination of the circulation time between the antecubital vein and the respiratory center.

In a series of cases it was found that accurate and definitive results were obtained with but simple preliminary preparation. The patient was placed in a supine position and 1.0 c.c. of a solution containing 0.25 Gm. of aminophyllin was injected as rapidly as possible into the antecubital vein. Timing was done with a stop watch and was calculated from the beginning of the injection to the first appearance of respiratory stimulation. Tabulation of the circulation times obtained in this series revealed a close approximation to the results obtained by the other methods that utilized either test materials with subjective end point or objective measurements with various photoelectric cells, ultraviolet light, or radioactive counters. The time in the majority (80.2 per cent) of these normal cases varied from 12 to 19 seconds, with an average time of 14.6 seconds. This method has special applicability in those cases where the ability of the patient to cooperate in the determination of a subjective end point may be limited by age, language difficulties, cerebral changes, or state of consciousness.

BELLET.

Wilson, M. G.: Immunologic and Biochemical Studies in Infants and Children With Special Reference to Rheumatic Fever. I. The Role of Genetic Susceptibility. Pediatrics **2**:239 (Sept.), 1948.

In rheumatic fever, susceptibility of the host is the important factor in the pathogenesis of the disease, and from epidemiologic and genetic studies it is concluded that this susceptibility is on a genetic and age basis. It is postulated that among families of known hereditary background there are children who are susceptible and not susceptible to the acquisition of rheumatic fever. The nature of the hereditary factors is obscure, but there are recent biochemical observations which demonstrate that such biochemical reactions as enzyme and protein specificities are gene determined. Perhaps in a susceptible child abnormal physiologic, chemical, immunologic, or hormonal responses may be present. If such endogenous factors were known, the role of possible exogenous agents might be clarified. Studies have been completed on complement titers and electrophoretic patterns in an attempt to evaluate immunologic response and possible differences in serum protein patterns among normal, susceptible, and rheumatic children. Other studies are in progress and it is hoped that information will be obtained as to the nature of the hereditable factors responsible for susceptibility to rheumatic fever.

JOHNSON.

Moore, R. L.: Treatment of an Infant With Paroxysmal Auricular Tachycardia. Pediatrics **2**:266 (Sept.), 1948.

A case of an infant with paroxysmal auricular tachycardia is described. At 20 days of age there were definite signs of heart failure and marked distress. He was digitalized by mouth with the tincture of digitalis, the dose being calculated as 0.2 c.c. per kilogram. After 0.6 c.c. was given, there was rapid improvement, and the greatly enlarged heart returned to a normal size. He was maintained on 0.1 c.c. daily, but within two to three weeks, symptoms recurred, and paroxysmal auricular tachycardia, confirmed by electrocardiogram, was diagnosed. Increased dosage of digitalis was without effect, and 0.5 mg. of acetyl-beta-methylcholine (Mecholyl chloride) was given intramuscularly. Within thirty seconds the baby became pale and cold, salivated profusely, and developed labored respirations. The heart rate suddenly slowed from 270 per minute to 40 to 50 per minute. The infant's condition improved in a few minutes with administration of 0.065 mg. atropine, intravenously. The pulse rose subsequently to 140 per minute and stayed there. The infant was maintained on 0.2 c.c. of the tincture of digitalis daily. At 3 months of age another paroxysm occurred. Increased digitalization was not effective and 2.0 mg. of Mecholyl were required to stop the attack, with the alarming side effects just described. Three weeks later, another episode occurred and quinidine was tried orally, starting with a dose of 20 mg. and with an increase of 20 mg. each two hours until, with a dose of 120 mg., the attack subsided. Further attacks required up to 180 milligrams. At the age of 5 months he had his last episode, which required 200 mg. quinidine for its control. From that time to the time of reporting at the age of 25 months he has been well, without evidence of cardiovascular abnormality.

JOHNSON.

Morgan, E. H., Allen, E. V., and MacCarty, C. S.: Acute Peripheral Circulatory Failure Caused by Acute Venous Thrombosis. Proc. Staff Meet., Mayo Clin. **23**:425 (Sept. 15), 1948.

Acute peripheral circulatory failure is a rare systemic effect of acute venous thrombosis. Manifestations include cold, pale, moist skin, tachycardia, hypotension, and the loss of peripheral pulses. Anemia and azotemia are additional features. This condition differs from the transient arteriospastic disappearance of pulsations in a limb following extensive acute venous thrombosis. Three cases of the more severe and generalized complication are described.

Although objective determinations of circulating blood volume and of limb volume were not made, it is the impression of these authors that a considerable quantity of blood, the equivalent of an extensive hemorrhage, had been trapped in the involved limbs as the result of acute venous thrombosis and that this caused peripheral circulatory failure in each of the three instances reviewed.

ARKLESS.

Woolsey, T. D., and Moriyama, I. M.: Statistical Studies of Heart Disease. II. Important Factors in Heart Disease Mortality Trends. Pub. Health Rep. **63**:1247 (Sept. 24), 1948.

Difficulties in determining the death rate due to heart disease in the past forty years are discussed. Changes in the terminology, changes in the rules for selection of primary cause of death, and the inclusion of more and more states in the registration area, as well as the gradually increasing age of the population, makes statistical evaluation difficult. At any rate, since 1930 when the registration area was virtually complete, the mortality due to heart disease has definitely increased for every age group over 45 years of age but has remained the same or declined in all the younger age groups. Over 45 years of age, however, there has also been a compensating decrease in the mortality from a certain group of causes of death closely associated with heart disease, such as intracranial lesions of vascular origin, nephritis, arteriosclerosis, and hypertension. When this entire group of cardiovascular, renal, and senility patients is studied, there is no consistent trend of mortality rate. It is possible that a true increase may have occurred in the risk of dying from one or more of the various forms of heart disease, and a true decline may have occurred in the rate of dying from intracranial vascular lesions and chronic nephritis. The fact seems apparent that for the group of diseases which reflect damage to the heart, kidneys, and arterial system resulting from hypertension and arteriosclerosis, the basic risk of dying for a person over 35 years of age is neither rising nor falling.

WAIFE.

Laufman, H., Martin, W. B., and Tanturi, C.: Effect of Heparin and Dicoumarol on Sludge Formation. Science **108**:283 (Sept. 10), 1948.

Using the technique of Kniseley, these authors during a course of vascular occlusion experiments in dogs were able to produce sludge at will and observe the result carefully. The sludge masses of blood cells may serve as a matrix for thrombus formation provided other conditions favorable to the development of thromboses are present. When anticoagulants are administered, thromboses do not generally occur in small vessels distal to an occlusion, but such doses do not prevent the formation of sludge.

The administration of anticoagulants prevents thrombus formation in the presence of sludge by preventing the sludged masses of cells from becoming adherent to the endothelial lining of the vessel. Sludge formation as such is not prevented.

WAIFE.

Rapport, M. M., Green A. A., and Page, I. H.: Crystalline Serotonin. Science **108**:329 (Sept. 24), 1948.

These authors report the isolation from beef serum of a crystalline substance which is vasoconstrictor in effect and which appears in connection with platelet destruction and the clotting process. It has been provisionally named *serotonin*. Chemical analysis shows that it is a sulfate which may also contain organically bound sulfur. It gives a positive test for nitrogen and a negative test for the halogens.

Injected intravenously into anesthetized dogs and cats, a solution of this material produced a rise in arterial pressure which was augmented in a sympathectomized animal. In a few animals small doses produced a depressor effect which became a pressor effect after the administration of tetraethylammonium chloride. The response after pithing was slightly reduced or unchanged. When the perfused isolated rabbit ear preparation was used, the vasoconstrictor activity of serotonin was more than twice that of an equal weight of epinephrine hydrochloride.

WAIFE.

Prinzmetal, M. Corday, E. Bergman, H. C., Schwartz, L., and Spritzler, R. J.: Radiocardiography: A New Method for Studying the Blood Flow Through the Chambers of the Heart in Human Beings. Science **108**:340 (Sept. 24), 1948.

Using a device which is essentially a Geiger-Müller counter with a direct-writing attachment, Prinzmetal and his associates have been able to study the passage of radiosodium through

the cardiac chambers. They obtained curves which record the concentration of radiosodium in the structures underlying the pick-up tube which was placed over the precordium. Small doses which are nontoxic were used.

In the normal, a curve composed of two peaks was obtained. The first was produced when the radiosodium was in the right heart; this peak declined moderately while the radiosodium was primarily in the lungs. The second peak existed when the radiosodium was in the left heart; this gradually disappeared. In cardiac enlargement, with or without failure, almost all curves have been monophasic, that is, one peak and fall.

Other observations revealed that the rate of venous return from the lower limbs was much slower than that from the upper extremities, and when radiosodium was injected as an isotonic solution intramuscularly, one-half of the injected solution was absorbed in thirty minutes and 90 per cent in one hour. Thus, the time required for absorption was much longer than would be anticipated. In hemorrhagic shock in dogs, intramuscular absorption of radiosodium was greatly prolonged. Theoretical concepts were confirmed in a study of the tetralogy of Fallot in which the right and left waves took the form that was anticipated from physiological studies.

WAIFE.

Hurwitt, E. S.: An Experimental Approach to the Problem of Increasing the Blood Supply to the Lungs. Surg., Gynec. and Obst. **87**:313 (Sept.), 1948.

The author describes an experimental technique to increase the blood supply to the lungs, particularly in the presence of pulmonary stenosis. Two avenues of approach were explored: (1) circumvention of the pulmonary valve by a shunt from the right ventricle to the proximal portion of the main pulmonary artery, and (2) dilatation of the pulmonary valve ring. In the shunt, polyethylene tubing was used. This is a chemically inert plastic substance which is light, malleable, flexible, easy to sterilize, and nonirritating to tissues. The experiments were performed upon eleven cats. Polyethylene tubing was successfully placed in three cats, although one died twelve hours postoperatively. One end of the pre-bent tube was sutured into the right ventricle, the other end into the pulmonary artery. Examination of two sacrificed cats showed no displacement of the ends of the tube. The lumen of the tube was occupied by a partially organized adherent thrombus. A thin fibrous membrane formed on the outer walls of the tube.

For dilatation of the pulmonary valve, the author used a tapered lucite prosthesis. This was inserted through an incision in the anterior wall of the ventricle of eight cats by a modified dura clip forceps. Three cats died immediately. In two cats the tube was not displaced; in one it migrated back to the ventricle, in one, to the bifurcation of the pulmonary artery, and in the third, to the hilus of the right lung.

The author suggests his experimental approach for the reproduction of the effects of valvular insufficiency and for the study of the altered physiology and dynamics of cardiac lesions.

BECK.

Barnes, C. G., Fatti, L., and Pryce, D. M.: Arterio-venous Aneurysm of the Lung. Thorax **3**:148 (Sept.), 1948.

Arteriovenous aneurysm of the lung is usually considered to be a rarity, and by 1942 only four examples were on record. Nineteen additional cases have been published in the last six years, however, and it is likely that as the clinical features of this syndrome become better known, still more of these cases will be separated from the cases of cyanotic congenital heart disease and polycythemia rubra vera, with which they are often confused. Two cases of this disease are discussed.

The outstanding feature of this syndrome is intense cyanosis; increasing dyspnea on exertion is the second symptom of which these patients complain, and which eventually incapacitates them. This appears to be due to stimulation of the respiratory center by the high carbon dioxide content of the arterial blood. In addition to these symptoms, hemorrhage may also cause these patients to seek advice.

Among the clinical features is the presence of an arteriovenous shunt in the pulmonary circuit which may sometimes interfere with physical development. Cyanosis and clubbing are marked. Examination of the heart reveals no abnormality, the blood pressure is normal, and the electrocardiogram either is physiological or shows slight right axis deviation without ventricular strain. The lungs are normal unless the aneurysm is large and situated near the costal surface of the lung, in which case a systolic murmur may be heard over it, sometimes continuing into diastole. Further physical examination reveals no abnormality, but the absence of splenic enlargement is important and may be the first feature to throw doubt on a clinical diagnosis of polycythemia rubra vera. A radiograph shows the heart to be of normal size and contour, and the lung fields clear, except for the shadow caused by the lesion itself.

The authors point out that differential diagnosis is sometimes difficult, since there are four conditions with which pulmonary arteriovenous aneurysm may be confused: cyanotic congenital heart disease, Osler-Vacquez disease (polycythemia rubra vera), bronchiectasis, and pulmonary tuberculosis.

Arteriovenous aneurysm, not a true tumor but a developmental malformation (hamartoma), requires surgical treatment in the form of pneumonectomy, lobectomy, or local excision. No medical measures will prevent the development of increasing dyspnea, and serious complications may occur if surgery is not undertaken. Small aneurysms can be excised from the lungs by the application of clamps around the aneurysm in such a way as to close its main supplying vessel last, thus allowing its expansile pulsation to demonstrate its outline. In the case of large aneurysms, a lobectomy must be performed, with dissection and ligature of the hilar structures.

The circulatory changes produced by removal of the aneurysm do not embarrass the patient, and no special measures, such as venesection, are needed either before or after the operation. The red cell count returns to normal within a few weeks, and cyanosis lessens rapidly during the week after the operation.

BELLET.

Sorgo, W.: The Intramedullary Section of Vasomotor Pathways as Treatment of Arterial Hypertension. Wien. med. Wchnscher. **98**:391 (Sept.), 1948.

In three patients suffering from essential hypertension a bilateral chordotomy as suggested by Foerster was performed. The operation consists of the resection of the vasomotor tracts at the level of low cervical or high thoracic segments. The pathways are supposed to be located in the middle of the anterolateral tract anterior to the pyramidal lateral area. Therefore, a deep section was made in the cord down to the gray matter. During or immediately following the operation the greatly elevated blood pressure fell considerably, in one instance to normal levels, to return to high figures within a few weeks or months. Disturbance of pain and temperature sensations made their appearance in all operated subjects.

BRUMLIK.

Jarisch, A., and Zotterman, Y.: Depressor Reflexes From the Heart. Acta physiol. Scandinav. **16**:31 (Oct.), 1948.

In anesthetized cats nerve action potentials from afferrent vagal nerve branches were recorded simultaneously with the electrocardiogram and with pressure changes within the right auricle. The recording system consisted of resistance-capacity coupled amplifiers for the nerve action potentials and balanced input amplifier for the electrocardiograms. A condenser placed in a high frequency circuit was used in recording intra-auricular pressures. Records were obtained by means of a multiple beam cathode ray tube. Slight traction excited auricular nerve endings which thus appeared to become active with each auricular contraction independent of auricular filling pressure although increasing intracavitary pressures were also followed by increased activity of these nerves, which resulted in cardiac slowing. The activity of the auricular branches could be separated from those serving ventricular muscle which on stimulation yielded smaller low voltage spikes. Their activity was greatly increased after clamping of the aorta or pulmonary artery. All fibers investigated appeared to have a high threshold to electrical stimulation (C fibers).

The authors concluded that their experienced did not support the assumption that cardiac distension elicits an accelerating reflex (Brainbridge), although large nerve fibers with lower electrical threshold possibly serving such a reflex may have been demonstrated. Their significance is still under investigation.

HECHT.

Menten, M. L., and Fetterman, G. H.: Coronary Sclerosis in Infancy. Am. J. Clin. Path. **18:**805 (Oct.), 1948.

The purpose of this paper is to add three cases of coronary sclerosis in infancy to the twenty-two previously recorded. The first case was a white infant boy, weighing nine pounds and one ounce at birth. X-ray study of the chest on the fifth day showed some enlargement of the heart. When the baby was 36 days old he weighed eleven pounds and one ounce, and the physical examination was negative. Regurgitation of feedings began at this time and continued for eleven days until one drop of tincture of belladonna was given before meals. When the baby was 54 days old he began to make grunting noises. The parents reported that the respiration increased gradually and that the infant's "color was bad." That afternoon examination by his physician revealed that his chest was clear, the heart rate was 130 per minute, and no murmurs were heard. The temperature was 99° Fahrenheit. The abdomen was slightly distended and became hard with each respiratory grunt. He quickly became worse; cyanosis increased and the grunting noises became more intense. Oxygen therapy did not help and the baby died. At post-mortem examination the heart was enlarged, weighing 42.0 grams. A minute subepicardial hemorrhage was present on the upper left ventricular wall at a point 1.7 cm. below the emergence of the anterior coronary artery. All of the superficial coronary branches were thickened, sclerotic, and calcified. In an x-ray film made of the heart after removal, the main coronary branches were clearly delineated by virtue of calcific deposition within their walls. An irregularly oval, pale yellowish-pink zone of softening, measuring 1.0 cm. in surface diameter, was noted on the anterior wall of the left ventricle just above the apex. It was rimmed by a dark red border. On section the lumina of the main coronary arteries appeared to be nearly obliterated. There was thinning of the wall in the softened area but there were no adherent clots. The aorta appeared diffusely thickened. Both internal iliac arteries were thickened and sclerotic. Several gastric mesenteric arteries were sclerotic.

The other two patients were siblings with almost identical histories. A similar fatal outcome occurred in both at approximately the same age. They were born and died in the same year. The first baby lived fifty-three days and the second child lived seventy days. A previous child had died under similar conditions at about the same age.

The arterial changes present in the three cases reported were well advanced and actually involved all three arterial coats. The authors state that no definite etiological factor has as yet been established for this condition. The presence of a large number of eosinophils in the adventitial and outer medial cellular infiltrates in sections of several of the sclerotic arteries in the first case lends some support to the theory of an allergic background. The occurrence of infantile arteriosclerosis in two siblings and its probable occurrence in a previous baby of this family would seem to implicate a congenital weakness of the elastic tissue in the arterial walls as a possible factor.

KLINE.

Apperly, F. L., and Cary, M. K.: The Control of Circulatory Stasis by the Electrical Stimulation of Large Muscle Groups. Am. J. M. Sc. **216:**403 (Oct.), 1948.

A simple method of aborting or preventing the peripheral circulatory failure of gravity shock is described. This consists in rhythmical electrical stimulation, applied to the muscles of the lower extremities. Used in thirty-two experiments in healthy adults from 23 to 58 years of age, it not only arrested the fall of pulse pressure and acceleration of heart rate associated with gravity shock, but it rapidly restored them to normal. When the stimulation was introduced before the patient was subjected to the hydrostatic effects of gravity, the symptoms and signs of gravity shock were prevented completely. That the peripheral circulation is retarded during gravity shock and

restored to normal by electrical stimulation was shown by the corresponding changes in circulation time from antecubital fossa to tongue, as illustrated in four subjects. The beneficial results were shown not to be the result of emotional disturbances consequent to the mild discomfort of the electrical treatment. The method is now being tried in the treatment of traumatic shock and as a preventive of postoperative shock, venous stasis, and thrombosis.

DURANT.

Hellems, H. K., Haynes, F. W. Dexter, L., and Kinney, T. D.: Pulmonary Capillary Pressure in Animals Estimated by Venous and Arterial Catheterization. Am. J. Physiol. **155**:98 (Oct.), 1948.

Through the right and left ventricles small branches of the pulmonary artery and of the pulmonary veins were catheterized in anesthetized dogs. The tip of the catheter was wedged into distal branches of the artery and veins so that the lumina of the vessels were completely occluded. The average pressure in the blocked pulmonary artery branch was 6 mm. Hg (range 5 to 8 mm.), while the simultaneous pressure in the pulmonary vein was higher by approximately four mm. Hg (6 to 14 mm.). Pulmonary artery pressure averaged 31/14 mm. of mercury. The slight differences in pressures between distal artery and vein were explained by the reduction of blood flow locally at the obstructed artery, and by slight local passive congestion at the site of the occlusion of the pulmonary vein. The pulmonary capillary pressures could thus be interpreted as averaging about 8 mm. of mercury. The pressures were higher during expiration than during inspiration, but the arterial-venous difference was maintained.

Pulmonary hypertension was produced by injection of Lycopodium spores through a third catheter inserted into a branch of the pulmonary artery of the opposite lung. The resulting pulmonary infarction raised pulmonary artery pressure from 31/14 mm. Hg to 76/38 and caused a corresponding twofold rise in the distal pressures.

HECHT.

Hiatt, E. P.: Effects of Repeated Oral Doses of Quinine and Quinidine on the Blood Pressure and Renal Circulation of Dogs With Experimental Neurogenic Hypertension. Am. J. Physiol. **155**:114 (Oct.), 1948.

Oral doses of quinine and quinidine (10 to 15 mg. per kilogram) were administered three times a day for several days to normal dogs and to four dogs with neurogenic hypertension. Plasma levels of 1.0 to 4.0 mg. per liter were obtained. In normal dogs renal plasma flow and glomerular filtration rate increased, without much change in blood pressure. In the hypertensive dogs renal circulation remained unchanged or actually increased, but a fall of blood pressure to near normal values was noted. Peripheral vasodilatation was thought to be the major cause of the pressure reduction. Quinidine depressed the blood pressure more than the quinine. The possibility that cardiac depression with lowered cardiac output may in part be responsible for the observed effects has not been excluded.

HECHT.

Williams, A. H., and Schroeder, H. A.: Asytolic Arterial Pressure Gradient as a Measure of Local Peripheral Resistance. Am. J. Physiol. **155**:132 (Oct.), 1948.

The asystolic arterial pressure gradient was defined as the descending curve of intra-arterial pressure following sudden occlusion of a major artery. This gradient was measured in the brachial, femoral, renal, and mesenteric arteries of anesthetized dogs through an intra-arterial needle connected to a Hamilton manometer. In some experiments the systemic blood pressure was measured simultaneously from another artery, and blood flow determined by a recording rotameter. Collateral circulation was sometimes occluded by a tight wire tourniquet around the proximal portion of the limb. The period of occlusion was brief, usually 8 to 12 seconds.

With the inflow into the artery cut off, the blood volume in the arterial segment steadily diminished. This resulted in the typical pressure gradient curve which showed initially a very

rapid fall of pressure, followed by a more gradual but steady decline. There were local differences in that the renal and mesenteric arteries showed a more rapid early fall in pressure than did the femoral and brachial arteries. Changes in the slope of the curve were thought to correlate directly with local peripheral resistance, a steep slope indicating low, a slow slope high resistance of local areas of circulation.

When vasoactive drugs were injected, the pressure gradients were altered so that following an intravenous injection of epinephrin the gradient was lowered (the slope of the fall being more steep) and the blood flow increased, indicating vasodilatation. This was followed by a rise in the gradient and decreased blood flow to show vasoconstriction. The vasodilatation known to follow sodium nitrite injection was demonstrated by a fall in the gradient. The measurements were thought to be quantitative if the collaterals were cut off by the wire tourinquet.

HECHT.

Shapiro, R., and Rigler, L.: Pulmonary Embolism Without Infarction. Am. J. Roentgenol. **60**:460 (Oct.), 1948.

Pulmonary embolism is now known to be a common complication of many diseases and operations. The increasing frequency of diagnosis is probably due to better diagnostic criteria and to the greater attention which this condition is receiving.

There is now sufficient clinical and experimental evidence to show that (in individuals with normal circulation) pulmonary embolism does not necessarily result in hemorrhagic infarction. In many of these cases, death ensues so rapidly that there is insufficient time for infarction to occur. There are, however, cases in which occlusion of a major pulmonary artery has been survived and with no evidence of infarction.

Westermark, following prolonged roentgen studies with autopsy control, has concluded that hemorrhagic infarction does not occur unless there is an occlusion of both the bronchial and pulmonary arteries. If only the pulmonary artery is occluded, infarction does not follow and the involved segment remains viable even though it may be unable to carry on any exchange of gases. He found that only 20 per cent of the cases in which pulmonary embolism was established at autopsy showed an associated infarction. In spite of these findings most roentgenologists still associate pulmonary embolism with an area of increased density in the roentgenograms.

In pulmonary embolism without infarction, the characteristic finding is ischemia of the involved pulmonary segment. This is represented on the roentgenogram by a segmental area of increased radiability. Central to the site of the embolism, the vascular pattern is well defined while in the area involved there is an abrupt termination of the vascular pattern. Often there is a sharp demarcation between the involved and uninvolved segments. The occluded vessel sometimes shows increased density up to the point of abrupt termination. The emboli without infarction may undergo organization and recanalization and be reabsorbed (leading to re-establishment of the circulation in the involved segment) or result in a retrograde thrombosis producing a larger area of ischemic involvement.

The roentgen changes of pulmonary embolism without infarction must be differentiated from those of partial bronchostenosis with areas of obstructing and nonobstructing emphysema.

The authors present three autopsy-confirmed cases of pulmonary emboli without infarctions. The clinical findings were those of emboli and the roentgen findings were those of emboli without infarction. Other cases of a similar character were observed but not reported since the patients survived and autopsy confirmation could not be obtained.

ZION.

Kerr, W. J.: Pathogenesis of Rheumatic Fever. Ann. Int. Med. **29**:587 (Oct), 1948.

The immunologic processes which are involved in rheumatic fever are not completely understood. Experiments concerning the development of auto-antibodies to various tissue extracts have suggested that the etiological agent, presumably the hemolytic streptococcus, by injury to or in combination with the connective tissues of the body produces auto-antibodies which act in vivo to bring about lesions in the living animal which may be progressive or may be reactivated by repeated exposure to the same organism. The reactions in the synovial membranes, subcutaneous tissues, cardiac valves, cardiac muscle, pericardium, lungs, and brain differ in the degree

of exudation so markedly that in some tissues the cellular components are not arranged in the compact masses which are seen so characteristically in the myocardium. The tissue reaction occurs as a small necrotic area around the small blood vessels and is made up of polymorphonuclear leucocytes and cells with a large basophilic cytoplasm. The latter cells are often multinuclear. There is a localized increase in vascularity. As the lesion progresses plasma cells and fibroblasts appear, gradually replacing the basophilic cells. The end result is a small area of fibrosis. The only tissues where lesions cause damage of a permanent progressive and crippling nature are in the heart. Why the proliferative features of the process assume such significance in the heart is unknown. The organization of the lesions in the valves and pericardium leads to mechanical disturbances which affect hemodynamics and lead to myocardial failure. The joints are seldom affected permanently. The kidneys may suffer chronic and progressive injury.

WENDKOS.

Wang, C. H., Bland, E. F., and White, P. D.: A Note on Coronary Occlusion and Myocardial Infarction Found Post Mortem at the Massachusetts General Hospital During the Twenty Year Period From 1926 to 1945 Inclusive. Ann. Int. Med. **29**:601 (Oct.), 1948.

Among 7,028 consecutive autopsies performed at the Massachusetts General Hospital between 1926 and 1945, inclusive, a total of 556 cases of myocardial infarction and 130 cases of coronary thrombosis without myocardial infarction were discovered. Of the 556 cases of myocardial infarction, 267 were recent and 289 were old and healed. The anterior wall of the left ventricle, supplied by the descending branch of the left coronary artery, was much the most common location of infarction, being almost twice as common as the posterior site, while lesions limited to the septum or right ventricle were quite infrequent. However, in seventy-two of the 190 hearts with fresh anterior myocardial infarction, there was an extension into the adjacent portion of the septum which was also true in thirty-five of the 109 hearts with fresh posterior infarcts. The size of the infarcts varied from 0.3 cm. by 0.1 cm. to 12 cm. by 15 centimeters. In many cases, the lesion involved the entire thickness of the wall but sometimes extended only one-half or three-fourths of the distance.

Only one-half of the cases of recent coronary occlusion showed infarcts. This supports the view that coronary occlusion and myocardial infarction do not always coincide and should not necessarily be considered to be synonymous. There was a lack of correlation between the site of the acute occlusion and the site of the infarct, which was presumably due to previous occlusions and the development of a collateral circulation. Large cardiac aneurysms due to myocardial infarction were found in 10 per cent of cases although aneurysmal concavities of small degree with shallow depression were commonly present. Both large and small aneurysms were the site of mural thrombi. Rupture of the ventricular wall at the site of an acute myocardial infarct occurred in less than five per cent of all these coronary cases. Both aneurysms and ruptures were preponderantly in the anterior wall of the left ventricle. In one case involving the septum, a ventricular septal defect resulted.

Of the 207 patients with thrombi in the left heart chambers, ninety-five (almost one-half) had complicating embolism of the cerebral, renal, splenic, or limb arteries or even of the aorta itself. There were half again as many patients with peripheral arterial block who showed no such thrombi in the left heart itself; evidently the embolus constituted the entire thrombus. Pulmonary embolism occurred in 106 cases, and could not be related in most instances to intracardiac thrombosis. Most often, it was due to an unrecognized thrombosis of one of the leg veins. Pericarditis occurred in about one-third of the acute and one-fourth of the chronic cases. It was always slight in degree.

In the total series, there were eighty-four patients who died within a few seconds to a few hours after the acute heart attack. Of these eighty-four patients, thirty-five showed fresh anterior myocardial infarcts; fifteen, fresh posterior infarcts; and thirty-four, acute coronary occlusion without infarction, eighteen of which involved the left coronary artery and sixteen, the right. Of another 108 patients who died of their acute heart disease within a few days but survived the first few hours, fifty-one showed anterior infarcts; twenty-six, posterior; twenty, both anterior and posterior; six, right ventricular alone; and five, septal alone.

WENDKOS.

Sigler, L. H.: Subjective Manifestations of the Hyperactive Carotid Sinus Reflex. Ann. Int. Med. **29**:687 (Oct.), 1948.

In 1,193 cases tested for hyperactivity of the carotid sinus reflexes, 970 (or 81.3 per cent) showed various subjective disturbances besides slowing of the heart rate and lowering of the blood pressure. In order of frequency, they consisted of dizziness, unconsciousness and convulsions, and abnormal sensation referable to the eyes, the vasomotor system, the sweat glands, the organs of sensation, the respiratory system, the somatic muscular system, the general constitutional state, the gastrointestinal system, and the heart. Individuals of the older age groups, especially those with cerebral arteriosclerosis, showed the greatest number and degree of disturbances. In some, the abnormalities occurred upon pressure on the carotid sinus of one side and not of the other. In others, the same abnormalities developed upon pressure on either one or the other side in the same patient but to different degrees. In still others, some symptoms developed with pressure on one side and other symptoms with pressure on the other. Unconsciousness and convulsions, with the associated manifestations due to the carotid sinus reflex, occurred in some of the patients who never had spontaneous attacks. Some patients gave a history of one or more attacks of spontaneous dizziness, fainting, or unconsciousness that was not due to demonstrable disease of the central nervous system but did not present these symptoms on carotid sinus pressure. Reflexes originating in other parts of the body presumably produced the same cerebral manifestations.

The underlying physiologic disturbances responsible for the various manifestations of the hyperactive carotid sinus reflex appear to occur in the central neurons or in efferent arms of the reflex arc, not in the carotid sinus receptors. For this reason, surgical removal of the nerve connections of the carotid sinus region cannot be expected to give relief in many cases, and whatever good results it may yield may not be permanent. It should be employed only in extremely serious cases of unconsciousness and convulsions which may be reproduced by the lightest pressure on the carotid sinus. Inasmuch as very serious complications may develop as a result of the test in individuals with cerebral arteriosclerosis, great caution must be used in performing the test in such individuals.

WENDKOS.

Cluxton, H. E., Jr., Bennett, W. A., and Kepler, E. J.: Anterior Pituitary Insufficiency (Panhypopituitarism—Simmonds' Disease), Pituitary Myxedema and Congestive Heart Failure (Myxedema Heart); Report of a Case and Findings at Necropsy. Ann. Int. Med. **29**:732 (Oct.), 1948.

Death in a 47-year-old man occurred following the relatively rapid development of severe congestive heart failure. During life, laboratory studies suggested the presence of thyroid and adrenal cortical insufficiency. Because of the neurological findings and a history of head injury, it was suspected that a post-traumatic atrophy of the pituitary gland was responsible for deficient formation of adrenotropic and thyrotropic hormones. An electrocardiogram showed low voltage of QRS and T-wave abnormalities in the limb leads, but not in the precordial leads. Necropsy revealed evidences of marked passive congestion in all organs as well as free fluid in the pleural, pericardial, and peritoneal cavities. Examination of the heart revealed dilatation and hypertrophy of the ventricles with interstitial fibrosis. There was no arteriosclerosis of the coronary arteries. The pituitary gland, the cortex of each adrenal gland, both lobes of the thyroid gland, and both testes were moderately atrophic. Hormonal factors were considered by the authors to be responsible for the structural changes in the heart and the subsequent myocardial failure.

WENDKOS.

American Heart Association, Inc.

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Telephone Plaza 7-2045

AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

Dr. Irvine H. Page, of Cleveland, has been elected President of The American Society for the Study of Arteriosclerosis. Other officers for the coming year are Dr. E. Cowles Andrus, Baltimore, Vice-president, and Dr. O. J. Pollak, Quincy, Mass., Secretary-Treasurer.

Directors elected are: (until 1952) Dr. Russell L. Holman, New Orleans, and Dr. Myron Prinzmetal, Los Angeles; (until 1951) Dr. Louis N. Katz, Chicago, and Dr. Henry S. Simms, New York; (until 1950) Dr. G. Lyman Duff, Montreal, and Dr. Joseph B. Wolffe, Philadelphia.

The Society, which will hold its annual meeting in Chicago on November 5-7 (see program in this issue), has prepared the following Statement of Policy:

> The purpose of the American Society for the Study of Arteriosclerosis is to further research, to improve methods of diagnosis and treatment, to work toward prevention, and to disseminate reliable information relative to arteriosclerosis.
>
> The membership is open to any scientist engaged in experimental or clinical research in the field of arteriosclerosis and related disorders. The Society seeks active cooperation with all organizations of similar aims or interested in related diseases and with any group which might be able to help in the solution of the urgent problem of arteriosclerosis.

ANNUAL MEETING OF THE GERONTOLOGICAL SOCIETY

The Annual Scientific Meeting will be held in Chicago, Nov. 5-7, 1949. The program has been arranged by Dr. William B. Kountz of St. Louis. On Monday, November 7, the session will be a joint one with the American Society for the Study of Arteriosclerosis.

SCIENTIFIC COUNCIL ELECTIONS

Dr. Tinsley R. Harrison, of Dallas, has been elected Chairman of the Scientific Council. This accords with the policy set a year ago to name as Chairman the immediate Past President of the American Heart Association. Dr. Harrison succeeds Dr. Arlie R. Barnes, of Rochester, Minn.

Dr. Carl J. Wiggers, Cleveland, was re-elected as Vice-chairman, and Dr. Lowell J. Rantz, San Francisco, was re-elected as Secretary.

Re-elected to the Executive Committee for three years are Dr. Kenneth G. Kohlstaedt, Indianapolis; Dr. Irvine Page, Cleveland; and Dr. Irving S. Wright, New York City. Re-elected to the Research Committee for five years are Dr. Ann G. Kuttner, New York City, and Dr. Lewis Thomas, New Orleans.

Dr. Harrison, Dr. Katz, Dr. George E. Burch (of New Orleans), Dr. Reno R. Porter (of Richmond, Va.), and Dr. John J. Sampson (of San Francisco), were named by the Council to one-year membership in the Assembly of the Association. Council members of the Board of Directors were noted in a previous issue.

REFRESHER COURSE PRESENTED AT UNIVERSITY OF VERMONT

A one-week refresher course for practicing physicians was conducted in June by the newly established Cardiovascular Unit of the University of Vermont Medical College. The course, comprising twenty-eight lectures, was presented at Bishop DeGoesbriand Hospital, in Burlington. Twelve faculty members participated and guest speakers were Dr. Paul D. White, of Boston, and Dr. Mercier Fauteux, of Montreal.

The Cardiovascular Unit began operations on July 1 and its investigative work is partly supported by funds from the National Heart Institute and the American Heart Association. Dr. W. Raab is its Director. Similar courses for postgraduate study are planned for the future for general practitioners in the northern New England area.

American Society for the Study of Arteriosclerosis

PROGRAM OF THE ANNUAL MEETING OF THE AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

TO BE HELD IN

CHICAGO, ILL., NOV. 6-7, 1949

IN COOPERATION WITH THE GERONTOLOGICAL SOCIETY

November 6, 1949*

Morning

(Irvine H. Page, Presiding)

9:30– 9:40 Opening Session

9:40– 9:55 **Observations on the Experimental Production of Arteriosclerosis in the Guinea Pig**
Dorothy Nelson and A. C. Ivy, Department of Clinical Science, University of Illinois, Chicago, Ill.

9:55–10:00 Discussion

10:00–10:15 **Rapid Production of Atheromatosis in Rabbits**
O. J. Pollak, Quincy City Hospital, Quincy, Mass.

10:15–10:20 Discussion

10:20–10:35 **Modification of Experimental Atherosclerosis by Means of Intravenous Detergents**
Aaron Kellner, James W. Correll, and Anthony T. Ladd, Department of Pathology, Cornell University Medical College, New York, N. Y.

10:35–10:40 Discussion

10:40–10:55 **Studies on the Inhibition of Experimental Cholesterol Atherosclerosis in Alloxan Diabetes in the Rabbit**
G. Lyman Duff and Torrence P. B. Payne, Department of Pathology, McGill University, Montreal, Canada.

10:55–11:00 Discussion

11:00–12:00 **The Biology of Arterial Tissue**
Jerome Gross, Department of Biology, Massachusetts Institute of Technology, Cambridge, Mass.

12:00–12:15 Discussion

Afternoon

(E. Cowles Andrus, Presiding)

2:00– 2:30 Business Session

2:30– 2:45 **Serum Lipids in Canine Arteriosclerosis**
Jack D. Davidson, Liese Lewis Abell, and Forrest E. Kendall, Goldwater Memorial Hospital, New York, N. Y.

2:45– 2:50 Discussion

2:50– 3:05 **The Pathology of Early Lesions in Experimental Canine Arteriosclerosis**
Margaret Bevans, Jack D. Davidson, and Forrest E. Kendall, Goldwater Memorial Hospital, New York, N. Y.

3:05– 3:10 Discussion

*The Gerontological Society will meet in an adjoining room.

3:10– 3:25 **Vascular Lesions in the Dog Following Thyroidectomy and Viosterol Feeding**

W. B. McAllister and L. L. Waters, Yale University, New Haven, Conn.

3:25– 3:30 Discussion

3:30– 3:45 **The Relationship of Blood and Liver Cholesterol to Atherosclerosis in Different Species**

H. J. Deuel, Jr., W. Marx, R. Alfin-Slater, and L. Marx, University of Southern California Medical School, Los Angeles, Calif.

3:45– 3:50 Discussion

3:50– 4:05 **Vascular Lesions in Experimental Hypertension**

A. C. Corcoran, Georges Masson, Beech Hazard, and Irvine H. Page, Research Division and Department of Pathology of the Cleveland Clinic Foundation, Cleveland, Ohio.

4:05– 4:10 Discussion

4:10– 4:25 **Histologic Sequence of Degeneration and Repair of the Rabbit Aorta Following Hypothermal Injury**

Bruce Taylor, David Baldwin, and George M. Hass, Rush Department of Pathology, Presbyterian Hospital, Chicago, in affiliation with the Department of Pathology, University of Illinois College of Medicine, Chicago, Ill.

4:25– 4:30 Discussion

4:30– 4:50 **Development and Metamorphosis of Cholesterol-Induced Atherosclerosis in the Chick. Effects of a Restricted Dietary Intake and of Cessation of Cholesterol Feeding**

L. N. Katz, L. Horlick, S. Rodbard, J. Stamler, and C. Bolene, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

November 7, 1949

Morning

(G. Lyman Duff, Presiding)

9:30– 9:40 Opening Session

9:40– 9:55 **Further Studies on the Action of Antilipfanogen in Preventing Fat Deposition**

Henry S. Simms, Columbia University College of Physicians and Surgeons, New York, N. Y.

9:55–10:00 Discussion

10:00–10:15 **The Etiology of Coronary Sclerosis in Chickens**

J. C. Paterson and G. E. Cottral, Department of Medical Research, University of Western Ontario, London, Canada, and the Regional Poultry Research Laboratory, United States Department of Agriculture, East Lansing, Mich.

10:15–10:20 Discussion

10:20–10:40 **Studies on Spontaneous and Cholesterol-Induced Atherosclerosis and Lipid Metabolism in the Chick. The Effects of Some Lipotropic and Hormonal Factors**

J. Stamler, C. Bolene, L. N. Katz, R. Harris, E. N. Silber, A. J. Miller, and L. Akman, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

10:40–10:45 Discussion

10:45–11:00 **Experimental Atheromatosis and Athero-hepatosis in Ducks and Geese; Its Reversibility and Clinical Implication**

Joseph B. Wolffe, Victor A. Digilio, Anthony D. Dale, George E. McGinnis, Daniel J. Donnelly, Mikhail B. Plungian, Joseph Sprowls, Frederick James, Claire Einhorn, and George Werkheiser, Wolffe Clinic and Hospital and Research Department, School of Pharmacy, Temple University, Philadelphia, Pa.

11:00–11:05 Discussion

11:05–11:20 **Simultaneous Studies on the Serum Lipids and the Electrophoretic Pattern of the Serum Protein in Man: Action of Inositol and Other Substances**
Irving Leinwand and Dan H. Moore, Department of Medicine, Post-Graduate Medical School of the N. Y. U.-Bellevue Medical Center and the Electrophoresis Laboratory, Columbia University College of Physicians and Surgeons, New York, N. Y.

11:20–11:25 Discussion

11:25–11:40 **The Vascular Problem in Diabetes Mellitus**
R. S. Megibow, H. Pollack, S. J. Megibow, J. J. Bookman, and K. Osserman, Mount Sinai Hospital, New York, N. Y.

11:40–11:45 Discussion

11:45–12:00 **Changes in the Cutaneous Arterioles in the Arm and Leg in Coarctation of the Aorta**
Edgar A. Hines, Jr., Eugene M. Farber, and Norman M. Keith, Mayo Clinic, Rochester, Minn.

12:00–12:05 Discussion

Afternoon

(Louis N. Katz, Presiding)

2:00– 2:15 **Does Arteriosclerosis Develop by Episodic Stages?**
Russell L. Holman, Department of Pathology, Louisiana State University School of Medicine, New Orleans, La.

2:15– 2:20 Discussion

2:20– 2:35 **The Use of Radioactive Sodium in Evaluating the Peripheral Circulation in Peripheral Arteriosclerosis**
Beverly C. Smith, New York, N. Y.

2:35– 2:40 Discussion

2:40– 2:55 **Prognosis in Abdominal Aortic Aneurysm**
J. Earle Estes, Mayo Clinic, Rochester, Minn.

2:55– 3:00 Discussion

3:00– 3:15 **Nature of the Hyaline Material in Arteriosclerosis of the Kidney**
Roger D. Baker and Sidney P. Kent, Department of Pathology, Medical College of Alabama, Birmingham, Ala.

3:15– 3:20 Discussion

3:20– 3:35 **The Principal Syndromes Associated With Cerebral Arteriosclerosis**
Frederic D. Zeman, Medical Department, The Home for Aged and Infirm Hebrews, New York, N. Y.

3:35– 3:40 Discussion

3:40– 3:55 **Results of Treatment of Coronary Arteriosclerosis With Choline**
Lester M. Morrison and William F. Gonzalez, Los Angeles, Calif.

3:55– 4:00 Discussion

4:00– 4:15 **Fat Absorption and Atherosclerosis: A Theory on the Development of Atherosclerosis With Ageing***
H. Necheles, Jacob Meyer, and G. H. Becker, Department of Gastro-Intestinal Research, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

4:15– 4:20 Discussion

4:20– 4:35 **The Effect of Estrogens Upon the Partition of the Serum Lipids in Female Patients**
Mary Lou Eilert, University of Chicago, Chicago, Ill.

4:35– 4:40 Discussion

4:40– 5:00 Closing Session

*May be presented in a Symposium on Nutrition at the Gerontological Society Meeting, November 5.

TO BE READ BY TITLE

Histology of Infarcted Heart Muscle
Rudolf Altschul, University of Saskatchewan, Saskatoon, Canada

Thyroid Activity and Tissue Cholesterol Distribution
Walter Marx and Lore Marx, Department of Biochemistry, University of Southern California, School of Medicine, Los Angeles, Calif.

The Hamster as Experimental Animal for the Study of Atheromatosis
J. Goldman and O. J. Pollak, Quincy, Mass.

A Method for the Estimation of 7-Ketocholesterol in Serum
Forrest E. Kendall, Walter Meyer, and Jack D. Davidson, Goldwater Memorial Hospital, New York, N. Y.

A Study of Atherosclerosis in Diabetes Mellitus
Joseph I, Goodman, Sigmund Wasserman, Louis J. Marcus, and Leonard Frankel, Mount Sinai Hospital, Cleveland, Ohio

Glomerular Obsolescence in Arteriosclerosis; Identity and Significance
J. F. A. McManus, Medical College of Alabama, Birmingham, Ala.

Aging As a Factor in the Renal Hemodynamic Response to a Standardized Pyrogen Test
Roger K. McDonald, David H. Solomon, and Nathan W. Shock, Section on Cardiovascular Disease and Gerontology, National Institutes of Health, Bethesda, Md., and Baltimore City Hospitals, Baltimore, Md.

The Silica Content of the Aortic Wall in Arteriosclerosis
E. Kirk and S. A. Kvorning, Division of Gerontology, Washington University School of Medicine, St. Louis, Mo.

Metabolic Studies in Coronary Thrombosis
Lester M. Morrison, Albert L. Chaney, William Gonzalez, and Perla Berlin, Los Angeles County General Hospital and the Department of Internal Medicine of the College of Medical Evangelists

Fat Tolerance Tests in Coronary Thrombosis
Lester M. Morrison, Perla Berlin, and William F. Gonzalez, Los Angeles County General Hospital and the Department of Internal Medicine of the College of Medical Evangelists

The Significance of Blood Serum Cholesterol Instability in Coronary Arteriosclerosis
Lester M. Morrison, Lillian Hall, and William F. Gonzalez, Los Angeles County General Hospital and the Department of Internal Medicine of the College of Medical Evangelists

The Effect of Crude Renal Extracts and Purified Renin on Vascular Lesions in Experimental Malignant Renal Hypertension
R. O. Burns, Jr., W. H. Jasper, and G. E. Wakerlin, Department of Physiology, University of Illinois College of Medicine, Chicago, Ill.

Fat Tolerance Curves in Rat and Rabbit Using I^{131}
G. Masson, O. Glasses, K. Savard, A. C. Corcoran, and Irvine H. Page, Research Division of the Cleveland Clinic Foundation, and the Frank E. Bunts Educational Institute, Cleveland, Ohio

The Effect of Graded Dosages of Iodide on Plasma and Liver Cholesterol of Normal, Cholesterol-Fed and Thyroidectomized Rabbits
Helen Bennett Brown and Irvine H. Page, Research Division and the Frank E. Bunts Educational Institute, Cleveland Clinic Foundation, Cleveland, Ohio

PROCEEDINGS OF THE AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

ABSTRACTS

OBSERVATIONS ON THE EXPERIMENTAL PRODUCTION OF ARTERIOSCLEROSIS IN THE GUINEA PIG

DOROTHY NELSON AND A. C. IVY, CHICAGO, ILL.
Department of Clinical Science, University of Illinois

There is at least one unidentified factor that is an essential nutrient for the guinea pig, in the absence of which these animals fail to grow, and die prematurely. If inadequate amounts of the factor are supplied, the guinea pigs survive for many months but develop severe pathologic changes, including arteriosclerosis.

Yeast, dried grass, and milk are thought to contain the unidentified factors (Elvehjem). Diets containing 30 per cent casein, 20 per cent cellulose, yeast, cerophyl, and liver extract promote good growth (Wooley). Crude casein contains a factor that increases growth and survival of pigs and which cannot be replaced by vitamin-free casein plus an excess of all the vitamins known in 1943 (King).

Our diet included all of these suggested factors for optimal development of the guinea pig. The cellulose in our diet was Ruffex. Recently Elvehjem and associates have found that gum arabic as 15 per cent of the diet is far superior to other forms of bulk and permits the reduction of casein to 20 per cent.

Arteriosclerosis develops slowly and most of our guinea pigs did not live long enough to manifest the condition. In some, however, the lesions were so advanced that they could be seen grossly and even palpated. The condition is not confined to the aorta. All of these pigs show liver, kidney, and adrenal damage together with damage of supporting tissues.

RAPID PRODUCTION OF ATHEROMATOSIS IN RABBITS

O. J. POLLAK, QUINCY, MASS.
Quincy City Hospital

Colloidal cholesterol suspensions dispersed in partially deproteinized rabbit's serum were injected intravascularly into rabbits.

Subintimal cholesterol deposits were observed immediately upon completion of injection of 65 mg. of fine suspension or as little as 5.0 mg. of coarse cholesterol suspension. Injection of larger amounts of cholesterol or modification of the volume of vehicle injected did not influence the results of experiments. Vascular alterations were seen in arteries of all calibers and also in veins; localization of lesions depended largely upon the site of injection.

While rabbits sacrificed immediately after injection showed numerous vascular alterations, animals examined sixteen hours after injection showed but few lesions. The number of atheroma-like lesions dropped to about one-tenth in rabbits allowed to survive for seven days after injection. Week-old plaques showed invasion with fibroblasts.

The lesions were larger upon injection of coarse suspension than when fine dispersed cholesterol was introduced. The number of plaques increased with multiple injections, as did the number of organized lesions.

Our observations suggest (1) that the initial lesions of experimental atheromatosis are due to intravascular precipitation of colloidal particles, (2) that these alterations are to a large extent reversible, (3) that resorption starts in about sixteen hours, (4) that subintimal deposits which are not resolved organize within approximately seven days, (5) that multiple episodes of dyscholesterolemia (a term used to characterize the dyscolloid state of cholesterol) have a cumulative effect. Vascular alterations produced by injection of colloidal graphite are indistinguishable from those initiated by injection of colloidal cholesterol. This suggests that atheromatosis is the result of a colloidal phenomenon, a nonspecific foreign body reaction in which intimal endothelial cells act as phagocytes.

MODIFICATION OF EXPERIMENTAL ATHEROSCLEROSIS BY MEANS OF INTRAVENOUS DETERGENTS

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The intravenous injection of the detergents Tween 80 or Triton A-20 into rabbits maintained on a cholesterol-free diet resulted in marked elevation of blood cholesterol and phospholipid levels and in the development of visible lipemia. It was possible by means of repeated intravenous injections of these detergents to sustain the elevated blood cholesterol and phospholipid levels for as long as twelve weeks. The blood phospholipid content rose parallel with the cholesterol in all cases.

The repeated intravenous injection of either Tween 80 or Triton A-20 into rabbits fed a high-cholesterol diet retarded or prevented the development of atherosclerosis. Groups of rabbits were fed a high-cholesterol diet and received Tween 80 twice daily or Triton A-20 twice weekly for nine to twelve weeks by intravenous injection. Control animals were fed the same cholesterol diet but received no intravenous detergents. The rabbits fed cholesterol and given intravenous detergents had far higher mean levels of blood cholesterol than the control animals, but significantly less atherosclerosis. The blood phospholipid levels of these animals were elevated in the same range as the cholesterol, whereas in the control animals phospholipid concentrations were invariably much lower than those of cholesterol. The incidence and severity of atherosclerosis was decreased if the blood phospholipid content was elevated concomitantly with the cholesterol. These studies suggest that the level of blood phospholipids may be an important factor in the development of experimental atherosclerosis.

Intravenous detergents were ineffective in the resorption of atherosclerosis previously produced by cholesterol feeding.

STUDIES ON THE MECHANISM OF THE INHIBITION OF EXPERIMENTAL CHOLESTEROL ATHEROSCLEROSIS IN ALLOXAN DIABETES IN THE RABBIT

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It has been previously shown by Duff and McMillan that the development of experimental cholesterol atherosclerosis is inhibited in alloxan diabetes in the rabbit. Two factors were observed to be consistently associated with this inhibition: the diabetic state and a degree of visible lipemia considerably greater than that observed in the control animals.

In an attempt to elucidate the mechanism of this inhibitory effect, the serum lipids were studied in normal and alloxan diabetic rabbits before and during the process of cholesterol feeding. One portion of each sample of serum was extracted with alcohol-ether for the determination of neutral fat and lipid phosphorus, and another with acetone-absolute alcohol for the determination of free and total cholesterol content. These represented absolute values. Another portion was dried from the frozen state in vacuo and extracted with cold choloroform, as described by Forbes and co-workers, and the content in this extract of neutral fat, lipid phosphorus, and free and total cholesterol determined. The lipids extracted in this way are referred to as the "readily extractable fractions" and are considered to represent lipids not bound, or only loosely bound, to the serum proteins.

It was found that in the transitory hyperlipemia which may occur in the early stages of alloxan diabetes in the rabbit, all of the serum lipid constitutents, but especially the neutral fat, were elevated. When cholesterol was fed following the subsidence of the spontaneous lipemia, there occurred an elevation of all the serum lipid constituents in both the normal and the diabetic rabbits. In the diabetic rabbits, however, the neutral fat showed a much greater rise in proportion to the increase in total cholesterol than it did in the normal rabbits.

In the normal animals the proportions of "readily extractable" lipid phosphorus and cholesterol were small while most of the neutral fat was "readily extractable." As the lipids became elevated during cholesterol feeding the "readily extractable fractions" tended to approximate the absolute lipid values in both the normal and the diabetic rabbits, although the approximation was somewhat more marked in the diabetics, that is a greater proportion of neutral fat was "readily extractable" in the diabetic rabbits than in the normal rabbits.

The factor that appeared to be most consistently associated with the inhibitory effect of alloxan diabetes on the development of experimental cholesterol atherosclerosis in the rabbit was the presence in the sera of the diabetic animals of a greater proportion of neutral fat in proportion to the level of cholesterol than in the normal control rabbits. It is suggested that the greater elevation of neutral fat in the cholesterol-fed diabetic rabbits is connected with mobilization of body fat associated with the diabetic state.

THE BIOLOGY OF ARTERIAL TISSUE

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The present paper will concern itself with one phase of the above-assigned title, namely the fine structure analysis of the components of arterial tissue. Among the constituents of the arterial wall, collagen, reticulin, and elastin have been intensively studied to date from the viewpoint of their macromolecular organization. The smooth muscle, endothelium, and cement substances have thus far received scant attention.

Collagen fibers are composed of bundles of fibrils whose diameters are below the resolving power of the light microscope. As seen with the electron microscope, these fibrils have a complex, axial repeating pattern with a period of 640 Angstrom units, which appears to be constant for collagen from all tissues of all the species of animals studied thus far. The collagen fibril itself is a parallel bundle of still thinner filaments bonded together laterally in a manner not yet fully understood. The strength of this lateral bonding appears to vary in different

tissues. The argyrophilic reticulin of the newborn rat aorta and rat skin appears to have the same characteristic cross-banded fibrils as does adult collagen, although these fibrils are considerably smaller in diameter.

Recent electron microscope studies of aortic elastic tissue have revealed large, branching fibers which are composed of bundles of trypsin-resistant, helically coiled threads imbedded in a trypsin-sensitive binding matrix. This general structure seems to be characteristic also of the elastin of other tissues. Inferences concerning the macromolecular architecture of elastic tissues may be drawn from physical properties such as thermoelasticity and force-extension relations. This aspect will be briefly discussed.

The possibilities and limitations of some of the biophysical techniques employed in a study of arterial tissue will also be discussed.

SERUM LIPIDS IN EXPERIMENTAL CANINE ARTERIOSCLEROSIS

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Most of the cholesterol in serum is not in true solution but is present in colloidal form, presumably stabilized by the phospholipids and serum proteins. Changes in the phospholipid-cholesterol ratio may be as important as hypercholesterolemia in the development of experimental arteriosclerosis. Therefore, data on the serum levels of free and total cholesterol, total lipids, and lipid phosphorus have been obtained on more than forty dogs on a regimen of thiouracil-cholesterol feeding.

Each dog was given 0.6 Gm. thiouracil daily and was fed a ration containing 5 per cent cholesterol *ab lib.* Blood samples were taken every two weeks for lipid determinations. Most of the dogs attained serum cholesterol levels of 1,000 mg. per cent or over within the first two weeks of the regimen and maintained high levels as long as it was continued. Values up to 5,000 mg. per cent were observed. A rise in total lipids and lipid phosphorus also occurred, but to a less marked degree.

In fifteen young dogs on a normal diet, the molar ratio of cholesterol and phospholipid was approximately 1:1. Following cholesterol-thiouracil feeding, the phospholipid increased at the average rate of one mol of phospholipid for every 5 mols of cholesterol.

Upon discontinuance of the thiouracil and cholesterol the serum levels of all the lipids declined at parallel and approximately exponential rates, reaching normal levels within one week.

THE PATHOLOGY OF EARLY LESIONS IN EXPERIMENTAL CANINE ARTERIOSCLEROSIS

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The efforts of the past year were designed to determine the length of time and the degree of elevation of serum cholesterol necessary to produce arteriosclerotic lesions in dogs on the thiouracil-cholesterol regimen and to study the sequence of histologic changes occurring in the formation and regression of the plaque.

In the dogs examined thus far, the degree of arteriosclerosis produced closely parallels the height and duration of the cholesterolemia maintained. It has been found that dogs sacrificed after two months of marked hypercholesterolemia

have macroscopic plaques especially marked in the thyroid arteries. Microscopic examination revealed these plaques to be due chiefly to accumulation of lipid in the media. Although the intima was laden with lipid, no proliferation of intimal cells was present. In dogs sacrificed after four months there were more widespread lesions showing beginning intimal proliferation, particularly in the arteries of the cephalad part of the body. In dogs sacrificed after six months the lesions were consistently more widespread and intimal proliferation was definite. In these latter dogs the arteries of the lower limbs were strikingly involved and there were indications that lesions in the fore part of the body had regressed despite continued hypercholesterolemia.

A number of dogs have been placed on a normal diet after a period of thiouracil-cholesterol feeding. Animals sacrificed at intervals of two to five months after their serum cholesterol levels returned to normal showed intimal proliferation as well as persistence of lipid in both intima and media in some arteries. In other arteries histologic evidence of regression of the plaque was thought to be present.

VASCULAR LESIONS IN THE DOG FOLLOWING THYROIDECTOMY AND VIOSTEROL FEEDING

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The arterial changes that follow thyroidectomy and the feeding of large quantities of viosterol have been reinvestigated. Widespread lesions of the aorta and coronary arteries appear in three weeks. The distribution of the aortic lesions duplicates that of intimal aortic sclerosis in man. The coronary arteries are regularly involved. The location of these lesions within the arterial wall is as often intimal as medial. Edema, hemorrhage, necrosis, and cellular inflammatory exudates are prominent components. Stainable lipid is present in many of the lesions, sometimes in association with acute inflammatory foci and sometimes in association with deposits of calcium salts. This lipid can be demonstrated after a few weeks of feeding. It is actively phagocytized. Accumulations of fat-laden foam cells appear in the intima of the affected vessels. Some degree of diffuse renal damage is regularly present.

The results of chemical examination of blood constituents (including lipids) of the experimental animals will be presented, and the significance of the morphologic and chemical findings briefly discussed.

THE RELATIONSHIP OF BLOOD AND LIVER CHOLESTEROL TO ATHEROSCLEROSIS IN DIFFERENT SPECIES

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The plasma and liver cholesterol levels and the histologic response of the aortas of rabbits, chickens, hamsters, guinea pigs, and rats were determined after the feeding of diets high in cholesterol for ten to sixteen weeks. Rabbits and chickens had the highest plasma cholesterol content while the cholesterol deposition in the liver of the hamsters far exceeded that of any other species. Significant cholesterol deposition and atherosclerosis occurred only in the rabbit and chicken while no evidence of such changes was found in the other groups. There appears to be no relation between liver cholesterol and susceptibility to atherosclerosis. Studies are being made on the relative rates of cholesterol turnover in different species with deuterium being used as a tracer.

VASCULAR LESIONS IN EXPERIMENTAL HYPERTENSION

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Hypertension was produced in rats by silk perinephritis, by administration of desoxycorticosterone acetate (DOCA) and by injection of a suspension of lyophilized anterior pituitary (AP). Rats given DOCA and AP were female, unilaterally nephrectomized, and they received 1 per cent sodium chloride as drinking water. Rats of the AP series were given a high-protein diet. Blood pressures were measured at regular intervals and the course of the hypertension was related to the vascular lesions.

It was shown: (1) That the lesions are similar in the three types of hypertension. (2) That lesions were present in all hypertensive animals and in some normotensive animals in the renal and DOCA groups. (3) That the type of lesion varies with the site; necrotizing panarteritis predominates in the mesenteric vessels; the heart shows either perivascular proliferation of reticulum cells with formation of granuloma or perivascular aggregations of cells with deeply staining nuclei and poor cytoplasm, the latter lesion resembling an Aschoff body; the kidneys show glomerulitis and arteriolonecrosis. (4) With DOCA, the first lesion is an accumulation of cells in the stroma of pancreas and mesentery. This appears when the rise in blood pressure is beginning.

HISTOLOGIC SEQUENCES OF DEGENERATION AND REPAIR OF THE RABBIT AORTA FOLLOWING HYPOTHERMAL INJURY

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Local lesions were produced in aortas of juvenile and senile rabbits with a hypothermal instrument cooled with expanding carbon dioxide. Animals were sacrificed at intervals during a period of twenty-four weeks thereafter and lesions were studied microscopically in serial sections. Degenerative and regenerative responses manifested a constantly changing pattern.

Aneurysmal dilatation occurred immediately after lesions were produced; inflammatory reaction was insignificant. Degeneration of smooth muscle cells in the media was apparent one week after injury and complete at two weeks. Elastic lamellae became straight, fused, and fragmented two weeks after injury. Medial calcification first appeared three weeks after injury and was complete at five weeks. In juvenile rabbits calcium in the media was slowly reabsorbed; in senile rabbits cartilage and bone replaced the calcium. Lesions of juvenile rabbits, after six weeks, were contracted; those of senile rabbits still showed aneurysmal dilatation.

Proliferation of the intima began in all animals at two weeks and was complete at five weeks. In juvenile rabbits the quantity of intimal proliferation was much greater than in senile rabbits. New formation of elastic tissue was observed in all animals in the thickened intima in lesions three weeks old. After twenty-four weeks, elastic fibrils in the proliferated intima resembled those of normal medial elastic lamellae. In all animals smooth muscle cells appeared in the thickened intima at two weeks. At six weeks they were as abundant and mature as those in normal media.

At four weeks, in all rabbits, a new internal elastic membrane began to form and was almost completely formed at twenty weeks. Since proliferated intima provided a matrix for new elastic tissue lamellae and smooth muscle cells, quantities of all elements were much greater in juvenile rabbits. Essentially, a new vessel wall developed within the framework of the proliferated intima.

DEVELOPMENT AND METAMORPHOSIS OF CHOLESTEROL-INDUCED ATHEROSCLEROSIS IN THE CHICK. EFFECTS OF A RESTRICTED DIETARY INTAKE AND OF CESSATION OF CHOLESTEROL FEEDING

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A study was undertaken to determine the physiologic parameters and preconditions of reversibility of avian cholesterol-induced atherosclerosis. For this purpose 5- to 8-week-old cockerels were fed 2 per cent cholesterol and 20 per cent cottonseed oil for ten weeks. Extensive atherosclerosis of the great vessels was observed in birds sacrificed at this time. Three groups were permitted to survive for another fourteen weeks on diets of (a) 2 per cent cholesterol and 20 per cent oil, (b) defatted chick starter mash, or (c) regular starter mash

Continuous cholesterol feeding over a twenty-four-week period resulted in a sustained hypercholesterolemia and increasingly severe aortic atherosclerosis. Microscopic studies showed increasingly heavy deposits of fat and cholesterol in the intima and media of the aorta, atheromatous "abscesses," and calcification. Cessation of cholesterol feeding resulted in a fall of the blood cholesterol to normal values within two to three weeks and a gradual diminution of grossly visible atherosclerotic lesions in both the low-fat (b) and normal (c) categories. There was no significant difference between the two groups. There was a marked tendency toward resorption of the less severe atherosclerotic lesions, with productive fibrotic and calcific changes in the more severe lesions.

The effect of a limited dietary intake (semistarvation) on lipid metabolism and atherogenesis was also investigated by giving a series of cockerels a diet approximately 50 per cent of that taken *ad lib* by a control group. This limited diet was supplemented with 4 per cent or 8 per cent cholesterol. On this diet growth and development were markedly retarded.

Serial plasma lipid fractionations revealed that these chicks, despite a grossly inadequate caloric intake, had a sustained hyperlipemia involving all elements, including cholesterol, phospholipids, and fatty acids. Correlated with this was a marked liver lipidosis and a high incidence of severe atherosclerosis of the aorta.

It is concluded from these studies that: (1) Under certain conditions atheromatous lesions are reversible. (2) In the chick, hyperlipemia and atherogenesis are dependent to a large degree upon the amount of ingested cholesterol; even conditions of relative starvation will not reverse these effects of dietary cholesterol.

FURTHER STUDIES ON THE ACTION OF ANTILIPFANOGEN IN PREVENTING FAT DEPOSITION

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THE ETIOLOGY OF CORONARY SCLEROSIS IN CHICKENS

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The evidence is reviewed that the primary lesion in coronary sclerosis of chickens is a focus of cellular infiltration and degeneration of the medial coat of the artery. The cause of the primary medial lesion has been sought, and the results of the various investigations are reported here.

Cholesterol feeding, infectious disease of an acquired type, and hypersensitivity to dietary agents have all been studied; but none of these appears to be of importance in the initiation of the primary lesion. On the other hand, evidence has been obtained which suggests strongly that the primary lesion of coronary sclerosis in chickens is a manifestation of lymphomatosis.

STUDIES ON SPONTANEOUS AND CHOLESTEROL-INDUCED ATHEROSCLEROSIS AND LIPID METABOLISM IN THE CHICK. THE EFFECTS OF SOME LIPOTROPIC AND HORMONAL FACTORS

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The combined effects of 1 per cent choline and 1 per cent inositol on lipid metabolism and on spontaneous and cholesterol-induced atherosclerosis were observed in cockerels over the course of twenty-five weeks. The lipotropic factors tended to aggravate the hyperlipemia and hypercholesterolemia and exerted a moderate, incomplete lipotropic effect on the fatty livers of cholesterol-fed chicks. Choline and inositol did not prevent, and actually tended to aggrevate, aorta lipidosis and atherosclerosis in cholesterol-fed chicks. In chicks fed regular mash, they had no effect on lipid levels and did not prevent early (six months) spontaneous atherosclerosis.

Pancreatectomized chicks fed regular mash exhibited no alteration in plasma lipid levels, and at fifteen weeks were free of spontaneous atherosclerosis. Cholesterol-fed pancreatectomized chicks exhibited alterations in plasma and organ lipids and in atherogenesis similar to unoperated birds given cholesterol. Apparently removal of the pancreas in the chick does not lead to the marked derangements in lipid metabolism and to the early vascular lesions observed in man.

The effects of thyroid and dinitrophenol on chick lipid metabolism and atherogenesis were compared in an attempt to clarify the mechanism of thyroid inhibition of cholesterol-induced hyperlipemia and atherosclerosis. Unlike thyroid, dinitrophenol had no consistent effect on plasma lipid levels nor on the frequency or extent of atherosclerosis in the cholesterol-fed chicks. It appears that the specific biochemical chain of events affected by thyroid hormone, and not hypermetabolism in general, is essential to alter lipid metabolism and atherogenesis in cholesterol-fed birds.

In chicks on regular mash, early spontaneous aortic atherosclerosis was observed as early as the fifteenth week of feeding either thyroid or dinitrophenol. Thus, unlike its effect on cholesterol-forced atherosclerosis, thyroid does not prevent, and may even aggravate, spontaneous atherosclerosis in the chick.

EXPERIMENTAL ATHEROMATOSIS AND ATHERO-HEPATOSIS IN DUCKS AND GEESE; ITS REVERSIBILITY AND ITS CLINICAL IMPLICATIONS

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Studies of the spontaneous occurrence of atheromatosis and atherohepatosis in wild ducks revealed the percentage to be extremely small as compared with domesticated Peking ducks, Muscovy ducks, and geese. Because of the ease of handling and feeding, the common goose was chosen for more extensive investigation. Atheromatosis and atherohepatosis were produced in forced-fed geese. A series of experiments are described showing the reversibility of this process by the use of diet, exercise, and pancreatic extract.

Pathologically the lesions produced in geese resemble atheromatosis in the human being, the most common variety of so-called "arteriosclerosis." The reversibility of the pathologic process adds further evidence to the rational of the use of diet, exercise, and, in selected cases, pancreatic extract in the treatment of atheromatosis and its many complications irrespective of the anatomic site of the vascular lesion.

Motion pictures of experimental work will be shown.

SIMULTANEOUS STUDIES ON THE SERUM LIPIDS AND THE ELECTROPHORETIC PATTERN OF THE SERUM PROTEIN IN MAN: (1) ACTION OF INOSITOL AND OTHER SUBSTANCES

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This project was concerned with the action of various substances such as choline, glucoronic acid, and pyridoxine, but chiefly with the action of inositol. A group of patients was selected who had clinical evidence of some disorder of lipid metabolism as indicated by clinical findings and confirmed by blood chemistry. The total lipids, fatty acids, lipid phosphorous, and cholesterol, were determined on the sera of these patients, and, simultaneously, electrophoretic patterns were determined before and after ether extraction. Inositol, 1.0 Gm. three times a day, was administered, without any attempt to control the diet and without other medications unless so noted. A decrease in total lipids and fatty acids with an increase in the lipid phosphorous and cholesterol was constantly produced in the earlier phases of treatment. As the period of treatment continued, there was a drop in the lipid phosphorous level and in the cholesterol. The only side reactions to the inositol are headache and gastrointestinal upset or diarrhea, which occurred in only a small percentage of cases. Since the production of a marked decrease in all lipids was accomplished by the use of inositol without diet, it is felt that the substance is a potential weapon against one of the probable factors in atherosclerosis.

THE VASCULAR PROBLEM IN DIABETES MELLITUS

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Present-day opinion stresses that the peripheral vascular lesions which occur in diabetic patients are indistinguishable pathologically from the arteriosclerotic changes which develop in nondiabetic subjects. The validity of this opinion was analyzed in a series of forty-eight diabetic patients ranging from 6 to 45 years in age. On the basis of accepted criteria (roentgenography, oscillometry, and vasomotor index), none of this group presented evidence of peripheral arteriosclerosis. An evaluation of the circulation by the microplethysmographic method following autonomic blockade with tetraethylammonium disclosed the unsuspected existence of structural vascular disease in twelve of these forty-eight patients. This was manifested by a decrease in the amplitude of the volume pulsations and a decrease in the rate of peripheral blood flow. The association of a normal oscillometric index and an abnormal microplethysmogram suggests that the fundamental peripheral vascular lesion in diabetes mellitus is a specific angiopathic alteration of the smaller blood vessels analogous, perhaps, to the vascular changes found in diabetic retinopathy or in the nodular variety of intercapillary glomerulosclerosis. The evidence implies that the primary mechanism responsible for the development of premature arteriosclerosis in diabetes may be related to mechanical rather than to metabolic factors.

In an attempt to elucidate the pathogenesis of the minute vascular changes, the plethysmograms have been correlated with various aspects of the diabetic state, namely, the level of the blood cholesterol, the insulin requirements, the presence of retinal and renal changes, and the severity and duration of the diabetes.

These investigations suggest that concepts previously entertained regarding the occurrence of vascular lesions in diabetes mellitus necessitate re-evaluation. Based upon this study, an analysis of the vascular problem in diabetes from the therapeutic and developmental standpoints will be presented in detail.

CHANGES IN THE CUTANEOUS ARTERIOLES IN THE ARM AND LEG IN COARCTATION OF THE AORTA

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Specimens of skin and subcutaneous tissue were excised for biopsy from the upper arm and calf of nine ambulatory patients who had coarctation of the aorta. The tissue was fixed in formaldehyde U. S. P. (1:10), blocked in paraffin, and stained with hematoxylin and eosin, elastin H, Van Gieson, and elastin-Van Gieson stain. To determine the degree of thickening of the arteriolar wall and the alteration in the wall-to-lumen ratio, measurements were made according to the method described by Kernohan, Anderson, and Keith. The first four arterioles in each slide were measured as the slide was moved from left to right. Most of the arterioles measured were located in the deeper portion of the cutis.

Thickening of the arteriolar wall and a decrease in the wall-to-lumen ratio as compared to normal were the characteristic findings in all cases. Study of each arteriole revealed structural changes consisting of endothelial hyperplasia, proliferation and thickening of the inner elastic lamina, hyperplasia of nuclear elements in the media, and apparent reduction in the size of the lumen. Not

all arterioles were equally affected, although most of the arterioles studied showed some changes from the so-called normal. The changes were similar to those previously observed in a study of the cutaneous arterioles of a group of patients who had essential hypertension. In the sections taken from the leg in this group of patients with coarctation the changes in the cutaneous arterioles were of the same degree as those taken from the arm.

DOES ARTERIOSCLEROSIS DEVELOP BY EPISODIC STAGES?

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There is no doubt that the incidence of arteriosclerosis increases with age, but this does not necessarily mean that the effects of age are causative, for other "scars" also accumulate with each successive decade. On the clinical side, it is generally recognized that many forms of human arterial lesions develop by episodic stages. On the experimental side, "crops" of arterial lesions can be produced in a matter of days, more or less at will, by a variety of procedures in several species of animals. Moreover, in the majority of cases these experimental procedures are as applicable to young as to old animals. In the light of these clinical and experimental observations it has seemed proper to inquire: Do the lesions dumped in the "wastebasket of arteriosclerosis" develop in a similar manner?

Recently the authors have started a systematic review of human arterial lesions with this question in the foreground. The meager data accumulated to date have confirmed previous observations. It is easy to find uniform early lesions whose clinical and anatomic features suggest development in episodic fashion in a matter of days. Further, it is not difficult to find cases with two or more "crops" of lesions; and, even in advanced arteriosclerosis, it is possible to pick out lesions of recent vintage. Some of these lesions will be presented.

From the studies thus far made it would appear that in all forms of arterial lesions, both human and experimental, there is good evidence for their development by episodic stages, and the tempo of the episodes is more in keeping with days than it is with decades.

THE USE OF RADIOACTIVE SODIUM IN THE DIAGNOSIS OF PERIPHERAL CIRCULATION IN PERIPHERAL ARTERIOSCLEROSIS

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Radioactive sodium, following its injection into the antecubital vein, can be followed throughout the body with a Geiger counter. The material is administered in amounts of 100 microcuries in 5.0 c.c. of distilled water. The half-life of radioactive sodium being 14.8 hours, the total exposure of tissue to gamma rays is less than 1 roentgen. The method has been employed in 2,000 cases without harm to patients or to those handling the material.

The time between injection and the demonstration of the arrival of radioactive sodium at any point in the body measures the circulation time between the points involved and has varied depending upon the degree of arterial occlusion.

Radioactive sodium leaves the plasma and eventually comes into equilibrium with the extracellular sodium in the body. The rate of this build-up has been determined in patients with and without arteriosclerotic peripheral vascular disease. In the presence of such disease the rate of transfer of the radioactive sodium from plasma to extracellular fluid has been found to vary from the normal.

The degree of variation has provided accurate clinical indications of the degree of occlusion of main and collateral channels, and, when charted in individual cases, has given more accurate information regarding the condition of main and collateral vessels than other tests in the same patients. It has also indicated prognosis, the effects of treatment, the probable benefit of surgery, and the type of surgery which local parts will tolerate.

THE PROGNOSIS IN ABDOMINAL AORTIC ANEURYSM

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Data were compiled from the records of 101 cases of abdominal aortic aneurysm, almost all of which were due to arteriosclerosis. These records were selected only when there was unequivocal evidence of aneurysm, and cases of true dissecting aneurysm were not included. Eighty-five per cent of the patients have been traced. From the present data it has been determined that 65 per cent of patients survived one year or longer after the date of the original diagnosis at the Mayo Clinic. Fifty per cent survived three years or longer, and 20 per cent five years or longer. These figures are approximate and may be altered by information subsequently obtained. However, it is not believed that they will be materially changed.

NATURE OF THE HYALINE MATERIAL IN ARTERIOLOSCLEROSIS OF KIDNEY

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The hyaline material appearing with arteriolosclerosis of the kidney is being studied by a variety of methods to attempt to determine its nature, or at least to compare it with the fatty and other components of larger arteries showing intimal atherosclerosis.

Extractability of the hyaline material varies, depending on whether the tissue is unfixed or fixed. For example, all of the material potentially stainable with Sudan black or Sudan III (which stain neutral fats) was removed in five minutes from the arterioles of unfixed kidney by treatment of frozen sections with acetone, and largely removed in one minute; while this same material, formalin-fixed, was not completely removed from frozen sections even after twenty-four hours of treatment by acetone. Using other methods, there was no difference between fresh and unfixed tissue. Finally, some of the methods required unfixed tissues.

The Sudan black and Sudan III stains indicate that the hyaline of the arterioles contains neutral fat, as do the plaques of intimal arteriosclerosis.

Application of a method for fatty acids (Fischer's method and Gömöri's method) indicated the presence of fatty acids in unfixed tissue. However, it is possible that hydrolysis had occurred during the post-mortem period or during refrigeration. The fatty acids in the hyaline arterioles are nearly all saturated, though a little unsaturated fatty acid is present (osmic acid stain), while in the atherosclerotic plaques of the aorta there were unsaturated fatty acids at the periphery of the plaques. Hyaline arterioles do not give positive staining for lipase, using Gömöri's method, while sections of liver prepared at the same time give a strong positive reaction.

Calcium was not identified in the hyaline arterioles of the kidney, using the Von Kossa method, but could be demonstrated in many of the plaques of the sclerotic aorta.

The hyaline material does not give the staining reactions of amyloid.

The periodic acid method colors the hyaline present in arteriosclerotic lesions, indicating the presence of carbohydrate (McManus, J.F.A.: Stain Technology, **23**:99, No. 3, 1948).

THE PRINCIPAL SYNDROMES ASSOCIATED WITH CEREBRAL ARTERIOSCLEROSIS

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In an effort to clarify the clinical picture of arteriosclerosis in the light of present-day knowledge, the various symptom complexes produced by diffuse and local involvement of the brain are presented. Each is discussed from the standpoint of the latent asymptomatic period, the period of functional insufficiency (partial occlusion or narrowing), and the period of functional failure (total occlusion). The effects of injury and of constitutional conditions, such as anemia and heart failure, are also emphasized with particular reference to the concept of cerebral circulatory compensation.

Among the syndromes that have been well established by the clinical and pathologic studies of many workers may be mentioned those affecting the anterior, middle, and posterior cerebral arteries, the superior cerebellar, the anterior inferior and posterior inferior cerebellar arteries, the vessels making up the circle of Willis, and the pressure changes caused by arteriosclerotic aneurysms. The relation of cerebral arteriosclerotic changes to the Parkinson syndrome and certain psychoses is also reviewed. The pseudoemotionalism seen after repeated cerebral accidents and the problem of cerebral vasospasm are discussed.

In conclusion, the favorable prognosis in some of these conditions and the good response to rehabilitation therapy is described in a few brief case reports.

RESULTS OF TREATMENT OF CORONARY ARTERIOSCLEROSIS WITH CHOLINE

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A series of 115 patients with proved coronary thrombosis and myocardial infarction were treated with choline after recovery from the acute attack and discharge from the hospital. These patients were divided into three groups: (1) Fifty-two patients given choline for one year, (2) a group of thirty-five given choline for two years, and (3) a group of twenty-eight patients given choline for three years. The dosage of choline varied from 6 to 32 Gm. daily. These series of patients were compared with a group of "alternate controls" consisting of 115 patients with proved coronary thrombosis and myocardial infarction who were discharged from the hospital under identical conditions. The patients in this series were observed over the same period of time and did not receive choline.

The detailed analyses of each choline-treated group as compared with its "control" series revealed that the subsequent mortality rate of patients was significantly reduced under choline treatment. The causes of death from recurrent coronary thrombosis and from cardiac congestive failure and the possible action of choline as a lipotropic agent in coronary arteriosclerosis are discussed.

These studies suggest that the lipotropic agent, choline, is of value in the treatment of coronary arteriosclerosis and merits further trial and observation in this disease.

FAT ABSORPTION AND ATHEROSCLEROSIS. A THEORY ON THE DEVELOPMENT OF ATHEROSCLEROSIS WITH AGEING

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In studies on the fundamental aspects of fat absorption we have observed conditions which may have a profound effect on the formation of atherosclerosis.

After ingestion of small quantities of fat, the chylomicron curves of twenty-five young and thirty older persons (average ages 18 and 76 years) showed a fundamental difference. In the young group, the count reached a maximum within two to three hours and returned to fasting levels at the fifth hour. In the older group, the counts rose continuously until the end of the twelfth hour and did not return to fasting levels until twenty-four hours had elapsed. These differences between old and young normal subjects developed gradually with age, and reached their maximum at an age of 50 years. The total number of chylomicrons was consistently and considerably higher in the older group. That the difference between the two groups was not due to disposition of fat by the body was shown by intravenous fat tolerance curves, which were similar for both young and old. Further tests have shown that older subjects on normal diets have a constant hyperchylomicronemia. This can be reduced to the level of young persons by the use of lipase preparations or detergents.

Chylomicrons are macromolecular bodies containing largely neutral fats but also cholesterol. Hueper, Moreton, and others have shown that macromolecular bodies can be deposited and can damage the internal layers of arteries. The neutral fats seem to disappear rapidly from the intima and subintima, while the cholesterol accumulates gradually, giving rise to the degenerative processes of atherosclerosis.

Our results on diminished digestive secretions, digestion, and absorption in older persons will be discussed in an attempt to explain the observed phenomena.

THE EFFECT OF ESTROGENS UPON THE PARTITION OF THE SERUM LIPIDS IN FEMALE PATIENTS

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Fasting total serum lipids, lipid phosphorus, and total cholesterol have been determined repeatedly on eleven female patients receiving estrogens for various reasons. The study included thirty control values when the patients were not receiving estrogens and forty-six determinations made during periods of estrogen administration. The group comprised one patient with still regular menses, three patients who had had normal climacterics, one patient who had had an artificial menopause by irradiation, and six patients who had had some form of surgical menopause. Periods of observation ranged from two weeks to twenty-six months. In several instances there were two or more control periods alternating with two or more periods of estrogen administration.

Eight patients received oral Estinyl in doses of 0.02 to 0.10 mg. per day, one received oral Stilbesterol in doses of 0.5 to 1.0 mg. per day, and two received 10,000 to 30,000 units of Progynon subcutaneously daily.

In all cases there was a sharp reduction in the ratio of total cholesterol to lipid phosphorus during periods of estrogen administration. This change was usually effected by an elevation of serum lipid phosphorus and a fall in total cholesterol; however, in one instance the average total cholesterol level was

unchanged, and in one it actually increased. In only one patient was the lipid phosphorus during periods of estrogen administration lower than the control values, but this was accompanied by a decrease in cholesterol sufficient to bring about some decrease in the cholesterol-lipid phosphorus ratio.

The possible relationship of the effect of estrogens upon the serum lipids to the lower incidence of arteriosclerosis in women, particularly before the climacteric, is suggested.

HISTOLOGY OF INFARCTED HEART MUSCLE

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Few authorities describe extensive regeneration of damaged skeletal muscle in adult mammals, the general opinion being that regeneration, if it occurs at all, is abortive. The regular enlargement and proliferation of muscle nuclei is considered by some as an indication of regeneration, by others as purposeless, "atrophic nuclear proliferation." I believe that the nuclear enlargement and subsequent nuclear amitotic division is due to a decompression resulting from the wasting of sarcoplasm. Observations on curarized and tetanized skeletal muscle confirmed this view (Altschul, R.: Arch. Path. **47**:223, 1949). In studying infarcted human heart muscle, I found that inside or in the vicinity of the scar tissue, nuclei of damaged muscle fibers are enlarged, sometimes nearly to the width of the single muscle fiber, but nuclear proliferation is very rare. Surprisingly, the muscle fibers are not markedly thinned. The nuclear enlargement may be caused by the same mechanism which leads to the formation of "muscle giant cells" or "nuclear tubes" in skeletal muscle, namely, the loss of pressure equilibrium between nucleus and sarcoplasm, with ensuing changes in osmotic pressure and imbibition of the nucleus. Although the moderate decrease in width of the heart muscle fibers does not conform with such an explanation, it may be that hypotonia of the damaged fibers is responsible for the nuclear expansion. It remains to be seen why the nuclei fail to divide after reaching the "critical phase" or why the latter is farther from the norm than in skeletal muscle. Comparing damaged cardiac with damaged skeletal muscle, it is concluded that the attempt at regeneration in the heart is less than in skeletal muscle or, contrarily, that by the steady contraction ("self massage") of heart muscle, the thinning of fibers and the "atrophic nuclear proliferation" are completely or partly prevented.

THYROID ACTIVITY AND TISSUE CHOLESTEROL DISTRIBUTION

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In a preliminary experiment, rats were fed cholesterol and bile salt, one group receiving in addition thyroid USP, and another group, thiouracil with the diet. Chemical determinations of plasma cholesterol levels indicated the expected changes, namely, low values for the hyperthyroid group (average, 39 mg. per cent) and high values for the thiouracil-fed animals (average, 251 mg. per cent). The cholesterol content of the liver, however, did not reflect cholesterol content of the plasma, but was very similar in these two groups (average values, 1.6 per cent and 1.5 per cent cholesterol, respectively). Histologic examination of the aorta revealed a slight cholesterol deposition in both experimental groups. In spite of the very low plasma cholesterol of the thyroid-fed rats, isolated small crystals were seen in most animals of this group, scattered through the endothelium of the aorta; otherwise, the structure of the aorta was normal. In the thiouracil-fed

group, the aorta had an entirely different aspect, showing a slight tendency to thickening of the intima associated with small localized cholesterol deposits. As far as could be estimated, not more, but, if anything less, cholesterol was deposited in the aorta of these hypothyroid rats, although the plasma cholesterol concentration in this group was appreciably higher.

Thus, neither the liver cholesterol content nor the deposition of cholesterol in the aorta appeared to depend upon the plasma cholesterol level. This might indicate that other factors play a role in the mechanism responsible for cholesterol deposition.

THE HAMSTER AS EXPERIMENTAL ANIMAL FOR THE STUDY OF ATHEROMATOSIS

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Sixty hamsters were fed 50 mg. of cholesterol powder (Armour) in gelatine capsules daily for from 30 to 130 days and thirty were fed a control diet without cholesterol. Several batches of hamsters of the same sex (male), age (3 months), and weight (90 to 100 grams) obtained from the same hamstery differed as to normal blood cholesterol values. One series had an average of 66 mg. of cholesterol per 100 ml. of blood and two other series had 142 mg. and 143 mg., respectively. Within each group of animals, the blood cholesterol values were fairly uniform. All three series of hamsters had an average liver weight of 2.36 grams and 600 mg. cholesterol per 100 grams of wet liver weight. There was, however, considerable variation in liver weight and liver cholesterol within each group of animals. In hamsters with low initial blood cholesterol values, both the blood and the liver cholesterol doubled after thirty days of feeding. In hamsters with a normally high blood cholesterol, the same effect was obtained, but only after sixty days of feeding. Upon further cholesterol feeding, the blood cholesterol level did not increase substantially, but after 130 days of feeding, the liver cholesterol was four times the original level. All cholesterol-fed hamsters had increased liver weight and liver steatosis reflecting the results of chemical analysis of that organ. Steatosis of suprarenal glands exceeded that of the liver. Parallel to the degree of steatosis, testicular atrophy was observed. Isolated subintimal foam cells were seen in the ascending aorta of but 10 per cent of cholesterol-fed hamsters. Some of these animals had marked, and others moderate, elevation of total blood cholesterol. None of the hamsters showed any appreciable degree of atheromatosis.

The golden Syrian hamster, therefore, seems ill suited for production of atheromatosis by feeding of cholesterol.

A METHOD FOR THE ESTIMATION OF 7-KETOCHOLESTEROL IN SERUM

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In the course of a study on the effect of possible cholesterol metabolites on the development of arteriosclerosis, a quantitative method for the determination of 7-ketocholesterol has been developed. Although this compound was not included in the list of oxidized sterols isolated by Ruzicka from arteriosclerotic lesions of human aortas, its presence there was indicated by the finding of Δ 3,5, cholestadiene-7-one, a substance formed when 7-ketocholesterol is treated with hot alkali.

The serum lipids are extracted with alcohol-ether. The fats are saponified in this extract with potassium hydroxide at room temperature in the presence of cyanide to minimize auto-oxidation and the nonsaponifiable lipid fraction is isolated. The oxidized sterol fraction is separated from the bulk of the cholesterol by the countercurrent distribution technique. The sterols are precipitated from alcoholic solution with digitonin; the precipitate is washed with alcohol and ether and then dissociated with pyridine. The digitonin is precipitated from the pyridine solution with ether. The ether solution containing the sterols is washed free from pyridine with dilute hydrochloric acid. The amount of 7-ketocholesterol present is estimated by measuring the optical density of the residue dissolved in absolute alcohol. Good recoveries are obtained when known amounts of 7-ketocholesterol are added to serum.

Application of this procedure to the sera of dogs with arteriosclerosis proved at autopsy shows the presence of a small amount of material precipitable with digitonin which has distribution coefficients and an ultraviolet absorption curve identical with those given by 7-ketocholesterol. In addition, upon treatment with hot alcoholic potassium hydroxide this material is converted into a substance having the ultraviolet absorption curve of Δ 3,5, cholestadiene-7-one which is formed when 7-ketocholesterol is treated in a similar way. These properties identify 7-ketocholesterol with a considerable degree of certainty.

A STUDY OF ATHEROSCLEROSIS IN DIABETES MELLITUS

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This paper is a report on eighty-nine unselected diabetic patients from Mt. Sinai Hospital of Cleveland in whom an attempt has been made to show the presence of atherosclerosis. Five diagnostic procedures were found to be of especial value: the carotid sinus pressure test, palpation of supraclavicular pulsations, the presence of calcification of the abdominal aorta as shown by roentgen study, the determination of occlusive arterial changes in the legs, and the presence of calcification in the aortic arch in chest films. The percentages of these diagnostic signs found in diabetic patients are evaluated and tabulated.

GLOMERULAR OBSOLESCENCE IN ARTERIOSCLEROSIS; IDENTITY AND SIGNIFICANCE

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With the periodic acid-Schiff reagent method it can be shown that arteriosclerosis, pyelonephritis, and glomerulonephritis alter the renal glomerulus in specific fashions. The recognition of the patterns of obsolescence which differ in these conditions allows the evaluation of the part played by each process in cases of renal disease. It does not explain the associated hypertension.

Arteriosclerosis produces knots of wrinkled basement membrane upon which hyaline has been deposited. The capsular space is filled in by another hyaline material. In the one scar, various stages of glomerular obsolescence are seen.

On the other hand, pyelonephritis involves the glomeruli by invasive inflammation, producing degrees of fibrosis of the tuft. Again, unlike arteriosclerosis, glomerulonephritis involves chiefly the glomerular capillaries, but epithelial crescents are formed after one week. Tubule-like organization occurs in the crescent. These "tubules" may persist beyond the obliteration of the glomerulus.

The changes in the glomerular basement membrane in arteriosclerosis can be interpreted as progressing in two phases. The original wrinkling might be the effect of ischemia as MacGregor suggested. The hyaline deposit could be derived from the circulating blood coursing at reduced speed through the ischemic glomerulus.

The arteriosclerotic or ischemic glomerulus is important from two aspects. In the first instance, fewer cases of "essential" hypertension would be so classified if the lesion were recognized. Second, observation of the developing glomerular lesion may provide clues as to the basis of the loss of kidney tissue in cases of arteriosclerosis.

AGEING AS A FACTOR IN THE RENAL HEMODYNAMIC RESPONSE TO A STANDARDIZED PYROGEN TEST

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Changes in glomerular filtration rate (GFR), effective renal plasma flow (RPF), and filtration fraction (FF) were evaluated following the intravenous administration of 50 million killed typhoid organisms in fifty-one men between the ages of 20 and 89 years. All subjects were normotensive and free from demonstrable cardiovascular or renal disease. The constant infusion technique was used for determining inulin and PAH clearances. Eleven twenty-minute urine collection periods were obtained following the administration of the pyrogen in three age groups: 20 to 49 years, 50 to 69 years, and 70 to 89 years.

The results obtained were as follows: No significant changes in the mean GFR were observed in any of the age groups following administration of the pyrogen. A marked increase was noted in the RPF of 363 c.c. (63 per cent of base line) in the 20 to 49 year age group; 349 c.c. (80 per cent) in the 50 to 69 year age group, and 223 c.c. (81 per cent) in the 70 to 89 year age group. The mean FF decreased from 19.7 to 12.1 (−38.6 per cent of base line) in the 20 to 49 year age group, from 21.0 to 12.7 (−39.3 per cent) in the 50 to 69 year age group, and from 23.4 to 12.7 (−45.7 per cent) in the 70 to 89 year age group.

Although it is known that the incidence and degree of renal arteriosclerosis and the mean FF increase with increasing age and the GFR and RPF are decreased in the aged population, it must be concluded from these observations that under the conditions of this study the renal arterioles of the aged individual can dilate as effectively as those of the young individual.

THE SILICA CONTENT OF THE AORTIC WALL IN ARTERIOSCLEROSIS

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A study was made of the silica content (SiO_2) of thirty-five samples of the thoracic aorta from individuals between the ages of 6 months and 96 years. For evaluation of the degree of arteriosclerosis, estimations were also made of the total ash, calcium, total lipid, and cholesterol content of the tissue. The adventitia was removed before analysis. Homogenization of the samples was obtained by treating the tissue with liquid air and subsequent grinding in a metal grinder. The silica determinations were performed by a modification of King's method.

The average silica content of the aortic wall was 14.0 mg. per cent and showed no definite change with age, whereas a marked rise was observed in the total ash, calcium, and cholesterol content with advancing years. The coefficients of correlation between total ash, calcium, total lipid, cholesterol, and silica were +0.15, +0.23, −0.10, and −0.13, respectively.

METABOLIC STUDIES IN CORONARY THROMBOSIS

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A series of studies was conducted on a group of fifty patients with recent coronary thrombosis and on a group of "control" patients, and normal individuals. These consisted of simultaneous determinations of (1) blood serum cholesterol, cholesterol esters, cholesterases, phospholipids, and total lipids; (2) serum albumin and globulin; (3) cephalin flocculation and thymol turbidity reactions for the beta and gamma globulins; and (4) blood iodine levels. All these determinations were carried out from one to three times in the same patients and comparative analyses were made of disturbances of blood plasma and serum lipid and lipid-protein relationships.

Abnormal, high elevations in the total blood serum lipids, the phospholipids, and the blood serum cholesterol levels are described and their clinical significance is discussed. A consistent disorder in the lipoid enzyme cholesterol esterase is analyzed and its clinical bearing in the patients with coronary thrombosis is discussed.

Instability of the blood serum and plasma lipids is described, as well as that of the beta and gamma globulins, in recent cases of coronary thrombosis.

The blood iodine levels are reported and their relationship to the blood serum cholesterol, lipid, and protein fractions is mentioned.

FAT TOLERANCE TESTS IN CORONARY THROMBOSIS

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A physiologic fatty meal consisting of a breakfast of eggs, bacon, bread and butter, coffee, and cream was administered as a "fat tolerance test" to a series of twenty-five patients with recent coronary thrombosis. The results were compared with those of a similar "fat tolerance test" performed on a series of normal individuals and on a series of patients suffering from miscellaneous diseases. Blood serum determinations were made of cholesterol, cholesterol esters, cholesterol enzyme esterases, phospholipids, and total lipids in the fasting patients, and hourly for four hours following the "fat tolerance" meal.

This investigation revealed that patients with recent coronary thrombosis have an abnormally high rise in the blood serum lipid constituents following the ingestion of a fat-test meal. Attempts are described to alter alimentary hyperlipemia by the use of fat dispersal or wetting agents as well as the use of lipotropic agents.

Simultaneous studies were carried out of chylomicron determinations in this series and the abnormal rises in chylomicron counts following fat tolerance tests are discussed in relationship to the behavior of the various lipid constituents discussed.

THE SIGNIFICANCE OF BLOOD SERUM CHOLESTEROL INSTABILITY IN CORONARY ARTERIOSCLEROSIS

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A. Thirty normal "control" subjects were tested on two or more occasions for the blood serum cholesterol content; this value was found to vary less than 10 per cent for periods up to one year.

B. Thirty patients suffering from miscellaneous diseases were tested for serum cholesterol under the same conditions; these cholesterol values were found to be subject to wide fluctuations.

C. Fifty patients who had recent coronary thrombosis were tested under the same conditions for periods up to one year; these patients with coronary arteriosclerosis were uniformly found to display wide variations in blood serum cholesterol content over periods up to one year.

D. Fifty patients with recent coronary thrombosis were treated with choline under the same conditions as the patients in (C) and studied for periods up to one year. Serum cholesterol determinations were made before, during, and after treatment with choline, and revealed uniformly wide and inconstant variations in cholesterol values. As many patients revealed increases as decreases in cholesterol values.

E. When determined by a reliable method, variation in blood serum cholesterol in an individual suggests the presence of a disease and/or some metabolic disorder.

F. Variations in serum cholesterol appeared to be directly related to the activity of cardiac lesions, with particular reference to coronary insufficiency and congestive failure. In these two latter states the instability of cholesterol was markedly increased when compared with that encountered in a group of patients who had experienced a coronary thrombosis three or more years ago and who were subsequently symptom free.

THE EFFECT OF CRUDE RENAL EXTRACTS AND PURIFIED RENIN ON VASCULAR LESIONS IN EXPERIMENTAL MALIGNANT RENAL HYPERTENSION

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Crude hog renal and liver extracts and purified hog renin were injected prophylactically into dogs subjected to simultaneous bilateral renal artery constriction previously found to produce consistent experimental malignant hypertension. Injections were made daily and intramuscularly for three months prior to and during survival or up to one month subsequent to renal artery constriction. Crude hog renal cortex extract containing renin was highly effective in protecting against the hypertension, at least partially effective against the arteriolonecrotic lesions, and partially effective in prolonging survival time (four dogs). Purified

hog renin was only partially effective in protecting against the hypertension and the arteriolonecrotic lesions and in prolonging survival time (four dogs). Crude hog whole kidney extract containing renin did not have an antihypertensive effect, and was only partially effective in protecting against the arteriolonecrotic lesions and in prolonging survival time (four dogs). Crude hog liver extract had no antihypertensive effect and was doubtfully effective in protecting against the arteriolonecrotic lesions of malignant hypertension and in prolonging survival time (three dogs). The mechanism of the antihypertensive effect is not yet determined. Antirenin may be involved. The mechanisms of the protection against arteriolonecrotic lesions and the prolongation of survival time remain to be determined. Present evidence suggests the possibility that the arteriolonecrotic lesions may be due to a renal necrotizing substance which is not renin. (A method which will produce consistent experimental malignant hypertension in the dog has been devised.)

FAT TOLERANCE CURVES IN RAT AND RABBIT USING I^{131}

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Iodinated cottonseed oil was given to both species by stomach tube in a dose of 7 c.c. per kilogram (0.1 c.c. of the oil yielded 8,000 counts per minute). Samples of blood were taken at regular intervals and blood fat was measured in terms of radioactivity.

The results showed a distinct difference between the two species. In both, the peak concentration was reached at approximately the same time (fifteen hours); in rats the rate of decay was rapid, reaching the initial concentration at forty hours, while in rabbits, hyperlipemia persisted for more than sixty hours. This difference in fat metabolism may be related to the production of experimental atheromatosis in rabbits and the inability to induce it in rats.

THE EFFECT OF GRADED DOSAGES OF IODIDE ON PLASMA AND LIVER CHOLESTEROL OF NORMAL, CHOLESTEROL-FED AND THYROIDECTOMIZED RABBITS

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Groups of rabbits (normal animals, normal animals fed cholesterol, normal animals fed iodide, and normal animals fed cholesterol and various dosages of iodide) were compared with similar groups of thyroidectomized rabbits. Cholesterol dosage was 400 mg. daily and iodide dosages 1, 5, 10, 20, and 40 mg. daily in normal animals and cholesterol-fed groups and 1 and 40 mg. daily in thyroidectomized and thyroidectomized, cholesterol-fed groups.

Normal rabbits and iodide-fed normal rabbits showed little change in plasma cholesterol. The concentrations were episodically increased by cholesterol feeding. Plasma cholesterol levels were further increased by iodide (1 mg. daily) during cholesterol feeding; larger dosages of iodide depressed the hypercholesterolemia. The greatest increase in plasma cholesterol was elicited by thyroidectomy with cholesterol feeding. In thyroidectomized, cholesterol-fed animals,

both 1 and 40 mg. iodide dosages depressed plasma cholesterol, the larger dosage having the greater effect. Thyroidectomy alone, with or without iodide, elicited a transient hypercholesterolemia.

Cholesterol feeding doubled hepatic total cholesterol in normal animals; this change was not affected by iodide, but was somewhat depressed by thyroidectomy. The proportion of hepatic ester cholesterol was doubled in cholesterol-fed normal animals. The increase in ester fraction was exaggerated by dosage with 1 mg. iodide; this effect disappeared with further increments of iodide dosage which tended to restore the proportion toward normal. Thyroidectomy alone, as well as iodide alone, decreased hepatic ester cholesterol fractions.

In conclusion, the effect of iodide on plasma cholesterol is variable and dependent on dosage in normal animals fed cholesterol, but wholly depressing in thyroidectomized, cholesterol-fed animals. The iodide has a similar action on the hepatic ester formation. Changes in hepatic ester cholesterol fraction tend to be concurrent with changes in total plasma cholesterol. The effect of iodide does not depend on the presence of the thyroid gland.